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HYPERTENSION ELECTROCARDIOGRAMS EXPERIMENTALLY PRODUCED AND ANATOMICALLY EXPLAINED.*

I. COR PULMONALE.

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A REVIEW of the subject of right heart failure, with an analysis of 210 articles concerning the causes, characteristic manifestations, and the mechanism of sudden death in clinical and experimental cor pulmonale, is now completed.[29c] This material may be summarized briefly: Cor pulmonale may be induced by any condition raising the pressure against which the right heart must empty itself. Most authors believe that the circulatory symptoms appear only after the right heart begins to fail and that the vast majority of cases never recover from their first breakdown. Whether right heart failure is primary or secondary, as when there is occlusion of a large pulmonary area, or when reflexes cause massive pulmonary arteriolar constriction or coronary constriction, the fact remains as stated by Fineburg and Wiggers:[10] "No evidence was discovered, or in our opinion has been presented by others, that circulatory failure following obstruction of the pulmonary circuit has any other cause than fatigue of the right ventricle."

Continuing the survey of cor pulmonale, we propose to discuss three additional problems: 1, the structural and functional anatomy of the right heart; 2, a review of electrocardiograms of cor pulmonale, both clinical and experimental, described in the litera-

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ture; and 3, electrocardiograms obtained experimentally by stretching the component muscles of the right ventricle.

1. **Structural and Functional Anatomy of the Right Heart.** The cardiac dissections of MacCallum,[22] Mall,[23] Tandler,[37] Shaner,[34] and others, showing that the right ventricle is mainly formed by the deep sinospiral muscle (DSS), whose fibers encircle it (parallel to the base of the heart) making both lateral and septal walls, have been repeated more recently by Robb,[28a] Flett,[11] and Lowe.[19a] The deficiency at the apex is partly filled by the superficial bulbospiral (SBS) which contributes mainly to the posterior papillary and less

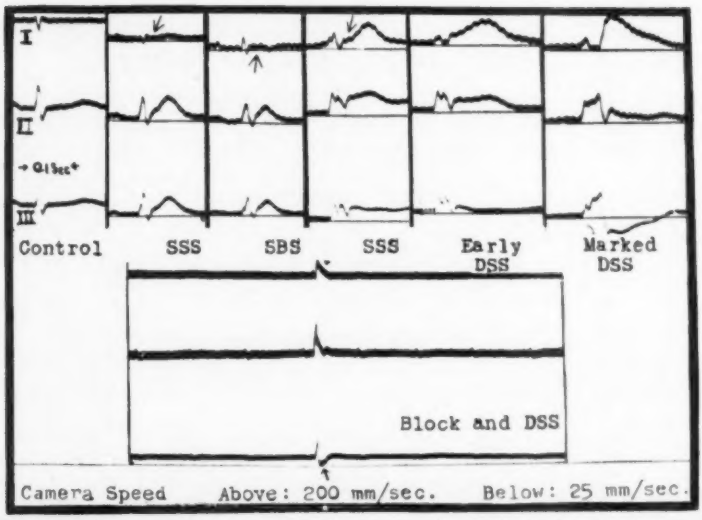

FIG. 1.—When the right ventricular pressure is gradually increased the first ECG change is slight elevation of S–T in all leads (superficial sinospiral). As the pressure increases further, S–T_1 is depressed and T_1 becomes negative, while S–T_2 is more elevated (superficial bulbospiral). The heart recovers and an SSS type recurs. Later, with beginning dilatation, S–T_1 is elevated while S–T_2 and T_3 become more negative. Finally, as death approaches, S–T_1 is greatly elevated and S–T_3 markedly depressed, also A–V block develops.

to the anterior papillary muscle (Shaner, p. 25[34]; Robb, Fig. 1, p. 288[28a]) and by the superficial sinospiral (SSS) which contributes mainly to the anterior and medial papillaries of the right ventricle (Shaner, p. 25[34]; Robb, p. 68[28a]). In previous experiments, it was shown that infarction of the two superficial muscles had no significant effect on blood pressure, whereas ligation of even a small blood-vessel supplying the deep sinospiral caused the blood pressure to fall greatly, and ligation of two or three branches to this muscle reduced the blood pressure to shock level. If a hollow organ is to "fail" or "fatigue" (Fineburg and Wiggers[19]), it will dilate and stretch the components of its walls, and obviously the weakest

component will fail first. The mass of the superficial sinospiral is least, hence it might be expected to fail before the others. This appears to be what happens, for many roentgenologists have reported that in right heart failure the earliest change is an increase in distance from the conus to the apex.[29c] When the next weakest muscle, the superficial bulbospiral, stretches, the apex will be even further from the conus. When these two muscles, which support the tricuspid valve leaflets *via* the chorda tendineæ, are overstretched a tricuspid murmur should develop. Thus Moschcowitz[24] writes: "In long standing cases tricuspid insufficiency results." Pollock[27] also mentions a "systolic bruit" which he thinks was a tricuspid murmur. Finally, when the deep sinospiral is stretched beyond its optimum tension, acute failure supervenes and transverse bulging is seen.

Robb,[28b] and Robb, Hiss and Robb[30] have shown that experimental acute infarction of these muscles produces a characteristic change in the electrocardiograms. Later studies apply these interpretations to human hearts with infarcts demonstrable at autopsy.[29b] Confirmation of parts of this work has been given by Lowe,[19a,b] who dissected the muscle bands in hearts after infarction and found that "Reconstructions of many of the scars show that they follow accurately the muscle planes and correspond to portions of one or more of the muscles which have been described." His Figure 16 presents an electrocardiogram in which S–T_1 is elevated and S–T_3 depressed, of which he writes: ". . . . in specimen 28 we have a tracing indicative of an anterior wall infarction according to the description just given, whereas reconstruction of the scar shows most of the damage to be in the walls of the right ventricle, lateral and posterior as well as anterior (Fig. XVI). In this instance the tracing seems to correspond to a muscle bundle rather than to an anatomical region such as Bohning and Katz[4] describe."

II. **Electrocardiograms in Right Heart Failure.** (*a*) Our review of electrocardiograms in cor pulmonale reveals only 14 published examples of the McGinn-White type. Let us first consider electrocardiograms in right heart failure associated with right ventricular hypertrophy in congenital hearts. Six of Abbott's[1] 7 cases we interpret as DSS muscle lesions. The seventh (Plate 13) is characteristic of an SSS lesion. All 7 of these electrocardiograms showed right axis deviation. In Schnitker's[33] data on 76 cases of right heart failure there was involvement of the SSS in 21%, of the SBS in 20%, of the DSS in 48%, and no typical muscle lesion in 11%.

Electrocardiograms labelled acute or chronic cor pulmonale are frequently seen in the literature,[3,9,14,15,20,21,26,31,38a,b] but the uniformity of these is not as great as in those cases with a chronic rise of pressure due to congenital heart disease.

In acute cor pulmonale McGinn and White,[21] and White[38a,b] describe a characteristic change of the electrocardiogram, namely:

"The presence of a Q-wave and late inversion of the T-wave in Lead 3, the rather low origin of the T-wave in Lead 1, usually a distinct S in Lead 1, and an upright* T-wave (with inverted P- and QRS-waves) in Lead 4." In some instances there is definite right axis deviation. Scrutiny of their electrocardiograms shows that only the crest of the S–T_3 reaches the isoelectric level. The beginning and end of the S–T_3 are depressed below the level of the T–P interval—this is especially well shown in their Figure 5. They state that these symptoms and signs are "due in large part to dilation and partial failure of the chambers of the right side of the heart." They mention the similarity of their electrocardiograms to those "due to occlusion of the R. coronary artery, the T_3 type." Barnes[3] also discusses this similarity and gives a table with points for distinguishing one from the other. Sokolow, Katz and Muscovitz[35] review 50 cases of cor pulmonale, classifying them according to the electrocardiogram. Their Table 1 arranges the data in four sections. Eight individuals did not survive pulmonary embolism: the electrocardiograms of 5 of these show S–T_3 depression, which is characteristic of lesions in the DSS muscle; the other 3 had SBS lesions in electrocardiograms taken from 3 to 8 days before death. Six records published are of those who survived; only 2 of these showed slightly depressed S–T_3 (Figs. 5 and 14). That 71% of those with deep sinospiral lesions died while only 43% with superficial bulbospiral lesions died, again supports the conclusion of Robb, Hiss and Robb[30] that lesions in the deep muscles have a graver prognosis.

Stewart, Kirk and Smith[36] have recently reported 12 cases of pulmonary infarction. Five of these patients died: 4 had repeated infarction before death and in the last electrocardiogram showed the DSS type of change; the fifth case seems to have died 30 hours after the first attack but the only electrocardiogram, an SBS type, was taken 13 hours before death. Here 80% of those known to show DSS lesions died (71% for Sokolow *et al.*[35]). Of 7 patients who survived, only 2 were seriously ill and these 2 had DSS lesions, whereas the others had superficial muscle lesions. These authors claim that the changes in the electrocardiogram are essentially those described by McGinn and White,[21] Barnes,[3] Langendorf and Pick,[17] Scherf and Schönbrunner,[32a,b] and feel that the electrocardiogram is useful in differential diagnosis. They emphasize the need of repeated tracings, saying: "The changes occur in rapid succession, the electrocardiogram reverting to its more usual form more quickly than in the case of coronary occlusion."

White[38b] (Figs. 69 and 71) shows electrocardiograms of acute and chronic cor pulmonale respectively. Both indicate a DSS lesion; they differ in that Figure 71 has a lower R_1, a deeper S_1, no Q_3, a higher R_3, and less convexity of S–T_3; they are alike in having low T_2, negative T_3, and in having slightly elevated S–T_1 and depressed

* Inverted with modern technique.

S–T_3 (the deep sinospiral type of electrocardiogram). The same type is seen in de Takats[8] (Fig. 8) taken 8 hours after pulmonary embolism, and also in his Figures 9 and 11, as well as in Rösler's[31] Figures 75 and 76. McCann[20] publishes a DSS type of electrocardiogram with the legend "record typical of that which occurs in hypertension of the pulmonary circuit."

In reviewing this extensive series of cases (not all of which were *acute* cor pulmonale), only 14 published examples of the McGinn-White type of electrocardiogram appear (McGinn and White,[21] 5 cases; Barnes,[3] Golden,[12] Knauer,[14] and Scherf and Schönbrunner[32a,b] (Case 6), each 1 case; and the 5 of Sokolow, Katz and Muscovitz[35]). It is not possible to tabulate or express as percentages the electrocardiographic variations reported in clinical papers, since sometimes the record is described but not published, S–T deviations are not always noted, the records are taken at variable times relative to the onset of symptoms and to death, seldom is a control record available to indicate any abnormality present before the pulmonary accident occurred, and finally, it is often impossible to determine whether the patient really had a cor pulmonale. Support of this opinion is contained in a personal communication from Dr. Paul D. White.*

Examples of superficial sinospiral and bulbospiral types of electrocardiograms were discovered, as were also many deep sinospiral cases. In no instance was a deep bulbospiral type (a muscle confined to the left ventricle) discovered either from published records or in descriptions of records not published. It would seem that a degree of increased pressure sufficient to cause a superficial sinospiral lesion in the right heart is not often diagnosed as due to cor pulmonale, and that among the cases diagnosed as cor pulmonale the greater proportion have deep sinospiral lesions.

(*b*) *Electrocardiograms from experimental work* are much more consistent. Buchbinder and Katz[6] produced right heart failure by injection of mercury into a leg vein, whence it passed to the heart and lungs, interfering with the lesser circulation. They also clamped the pulmonary artery in some experiments. Their Figures 4, 5, 6 and 7 are predominantly deep sinospiral lesions.

Krumbhaar[16] also did acute experiments during which the pulmonary artery was clamped and later released, which resulted in electrocardiograms of the deep sinospiral type. His Figure 2 of Experiment 7 shows S–T_1 elevated while S–$T_{2,3}$ are depressed after a moderate degree of occlusion. With a greater compression of the artery, S–T was depressed in all three leads. Krumbhaar's Figure 4 (third, fourth, fifth series) shows elevation of S–T_1 and

* "It is very important to note that many cases of pulmonary embolism do not have the acute cor pulmonale—most are too slight and some are too severe (causing death in *shock*). Few are studied at just the right time or degree to show what I consider the typical acute cor pulmonale, hence the majority of Katz's electrocardiograms are not comparable with ours, nor are ours all of the same degree."

depression of S–T_3, which changes, up to a certain extent, were reversible. Holman and Beck[13] in an experimental study of aortic and pulmonary stenosis publish one electrocardiogram from their Experiment 4 with pulmonary stenosis of 5 months' duration. Right axis deviation is present as is also elevation of S–T in all leads (SSS; see also their Fig. 2, Part I).

Anderson[2] reporting experimental work mentioned disturbance of the S–T segment. Otto[25] was mainly concerned with changes in the T-wave and unfortunately did not take three leads in all experiments. Criep[7] also did not take all three leads constantly but does write: "All showed a negative T_2 with shortened R–T interval and T starting either above or below the line." He concludes that vagal effects are unimportant and believes the changes to be asphyxial. Love, Brugler and Winslow[18] report depression of all S–T segments (DSS) as a constant finding and related these changes to dilatation of the right ventricle.

III. **Experimental Study of Acute Cor Pulmonale.** Experiments during which the right intracardiac pressure was gradually but progressively raised up to the point of acute failure were performed to study the apparent similarity between electrocardiograms of right-sided heart strain and muscle bundle lesions produced by ligation of specific coronary supply.

Method. Dogs and rabbits were anesthetized with appropriate doses of soluble pentobarbital, artificial respiration instituted and the thorax opened. For the study of the two ventricles 15 animals were used. Electrocardiograms (three simultaneous leads recorded either on a crystal galvanometer built by the Cambridge Instrument Company[29a] or by three string galvanometers recording simultaneously) were taken during anesthetization, also after opening the thorax and at intervals after compression of the pulmonary artery.

Results. Considerable compression could be applied before any effect was noted. Beyond a critical point, the heart elongated from the conus to the right apex. With still greater pressure the transverse diameters of the right heart increased, the ventricle "ballooning" out. With almost complete occlusion of the pulmonary artery the left heart was firmly contracted, small and empty. Only with sudden great asphyxia did the left heart dilate after the right heart had done so. Terminal arrhythmias were uncommon. All hearts eventually slowed, even though the vagi were cut. The immediate effect on the electrocardiogram was to raise the S–T slightly in all leads above the T–P isoelectric level (+++* superficial sinospiral type). A second stage followed in which S–T_1 was depressed and S–T_3 further elevated (−++ superficial bulbospiral added). Still later S–T_1 elevation returned while the S–T_3 was as much depressed as the S–T_1 was elevated (+−− deep sinospiral) (Fig. 1). The

* + or − signs refer to displacement of RS–T interval upward or downward, respectively, from the T–P isoelectric level, in Leads 1, 2, 3, respectively.

occurrence and duration of these stages varied with the degree of constriction. With sudden very excessive increase of pressure, the S–T in all leads was depressed (SBS plus DSS). In no instance did a DBS type (very great elevation of S–T in all leads, characteristic of lesions in the deep bulbospiral muscle which is entirely confined to the *left* ventricle) occur in right heart failure. Right axis deviation was not observed in the acute experiments. This observation confirms that of experimental work by Buchbinder and Katz[6] and accords with the clinical findings of Stewart *et al.*,[36] where in 12 cases of cor pulmonale right axis deviation was found but twice. Right heart failure, then, gives a *terminal* electrocardiogram quite different from that of left heart failure. (See Part II, p. 634, this Journal.) Moreover, this type is the one found to be characteristic of injury to the deep sinospiral muscle.

IV. **Statement of Problem for Discussion.** Our experiments indicate that in right heart failure the three component right ventricular muscles fail consecutively. This is shown by direct observation, by Roentgen ray reports as previously quoted,[29c] and by electrocardiograms. When pulmonary pressure is increased, the distance from the pulmonary conus to the right apex (outflow tract) becomes greater. The earliest electrocardiographic changes indicate injury first to the superficial sinospiral and presently to the superficial bulbospiral muscles. It is an accepted anatomic fact that the right apex is formed by the intertwining slender portions of these two muscles. As fluid pressures within a cavity are equal in all directions, the weakest region must obviously stretch first (*i. e.*, the apex). Only when the stronger, deep sinospiral fails will the transverse diameters at the base of the right heart increase. Injury to each muscle results in a characteristic effect on the electrocardiogram. Given that the electrocardiogram will reflect previous myocardial damage, together with summation effects for each muscle acutely involved, one can explain why there are so many divergent reports of the electrocardiogram in cor pulmonale. A most important consideration is time. In acute experiments one watches the beam of light continuously, taking frequent records and thus a smooth progression showing each stage of involvement is obtained. In practice, the sicker the patient, the less is the probability of frequent and especially of terminal electrocardiograms being taken. With so many variables, it would be astonishing indeed if there were much similarity between clinical electrocardiograms.

One might mention the custom of neglecting S–T deviations of less than 1 mm. It is a fact that action currents record maximally if they pass parallel to the plane in which the electrodes are placed and record not at all if they pass at right angles to the axis of the electrodes. *Absence of large galvanometer deflections in the latter instance is no proof of tissue inactivity.* Thus when the three standard leads are recording cardiac currents, they are often oriented

so nearly at right angles to certain portions of the heart that activity in these areas fails to register (producing so-called silent areas). More recent work with chest leads has proven these are not actually "silent" areas. The minimal displacements have a significance which is generally not admitted. It would be equally amateurish either to diagnose and to make a serious prognosis from every minor deviation of S–T (less than 1 mm.) or to neglect such minor deviations for analysis and localization. Bourne and Evans[5] found that 17% of 80 anginal patients showed electrocardiographic evidence in Lead IV only and they concluded that "Lead IV helped to emphasize the importance of *slight* changes in Leads I, II and III . . . ."

Summary and Conclusions. 1. Electrocardiograms taken in experimental right heart failure agree in form with those of previous authors.

2. Whatever the cause, pulmonary hypertension, if immediately great, may produce acute right heart dilatation, or if sufficiently prolonged, results in right heart hypertrophy and eventually in failure.

3. The essential mechanism of failure consists in the progressive stretching of the three component muscles of the right ventricle. The weakest area at the right apex is formed by the superficial sinospiral muscle and strain of this muscle is heralded by some elevation of RS–T in all leads. A second weak area, the superficial bulbospiral portion of the apex becomes involved and this is recognized by further elevation of RS–T in Leads 2 and 3 and coincident depression of S–T in Lead 1. Widening at the base indicates failure of the deep sinospiral and is evidenced by marked depression of RS–T in Leads 2 and 3, and either elevation or depression of RS–T in Lead 1, depending on the degree of concomitant superficial bulbospiral involvement.

4. It is immaterial whether the exciting cause of muscle failure is rise of pressure within the right heart or whether failure is secondary to asphyxia produced either directly or reflexly. When these muscles are under tension and unduly stretched the same electrocardiographic picture is produced as if the muscle were infarcted or otherwise damaged.

5. Because these muscles fail consecutively and because damage to each has its own effect on the electrocardiogram, and especially because there may have been preëxisting disease (or effects due to drug action), a valid explanation is available for the great variation in clinical electrocardiograms during an attack of cor pulmonale.

6. In these experiments, with the chest open, a dilated right heart was not associated with right axis deviation.

7. The McGinn-White type of electrocardiogram is probably associated with a moderately severe degree of rise of intracardiac pressure, stretching all three of the component muscles. When intracardiac pressure is dangerously increased, all S–T intervals are

depressed *in addition to some one or all of the changes described by McGinn and White, Barnes, or Rösler.*

8. If intracardiac pressure increases slowly and not too greatly, the electrocardiogram may be wholly unaffected, or if the pressure increases are rapid and extreme, any combination of muscle injury pictures may occur, thus accounting for the variable reports concerning electrocardiograms in pulmonary embolism and hypertension.

9. The employment of muscle bundle localization may serve to increase the value of electrocardiograms in the recognition, treatment and prognosis of cor pulmonale.

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HYPERTENSION ELECTROCARDIOGRAMS EXPERIMENTALLY PRODUCED AND ANATOMICALLY EXPLAINED.*

II. Left Ventricular Strain.†

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It is well known that the electrocardiogram is frequently altered in systemic hypertension. Shift of the apparent electrical axis to the left, displacement of the S–T segment (generally downward in Lead 1 and upward in Lead 3), negativity of T_1 and positivity of T_3 are regarded as characteristic. No explanation for such signs has been substantiated. Current teaching is summarized by Best and Taylor[4] (p. 303) who describe these changes in the electrocardiogram associated with hypertension and offer three theories in explanation:

"(1) That it is due to the *greater mass of muscle*, the electrical changes occurring in the hypertrophied chamber overbalancing those of the normal side. This theory has been rendered untenable by the discovery that the electrocardiographic features which were thought to be produced by one ventricle are actually produced by the other (p. 312). In other words, the electrical changes in the *sound* ventricle overbalance those of the hypertrophied side." Master[9] apparently adheres to this hypothesis, believing the electrical signs are gradual developments due to the increasing size of the left ventricle. In his own series of 152 patients with hypertension, 117 (74%) presented left axis deviation. He emphasizes that changes were gradual and depended "on the duration of the hypertension and the degree of enlargement of the left ventricle and not on changes in the heart muscle" (p. 91). He also writes (p. 92): "The changed anatomical configuration of the muscle masses may alter the time of onset of regression of the electrical excitation wave in specific tissues like the bundle branches or in the myocardium itself and thus may produce characteristic electrocardiograms in the

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† Strain is defined as: A forcible stretching, tending to alter shape, an injury to a muscle due to excessive tension or use.

standard leads." On page 94, he mentions that "the duration of the QRS complex is normal and there is neither notching or slurring which often occurs in myocardial involvement" and again on page 100, "However, the widened, slurred and notched QRS complex and the large initial negative deflection in lead IV (deep Q4) indicate involvement of the myocardium."

"(2) *Altered position of the heart.* The greater mass of the hypertrophied ventricle causing rotation of the heart around its longitudinal axis; this probably plays only a minor rôle.

"(3) *Slowed conduction* over the bundle branch supplying the hypertrophied ventricle as a result simply of the lengthening of the conduction pathway incident to the enlargement of the ventricular cavity, or to actual injury of the conducting tissue associated in some way with the cardiac disease. According to Barker[1] and associates, one or other of these factors is the most probable explanation of the characters of the electrocardiogram in ventricular hypertrophy."

Barnes and Whitten[2] agree with Barker *et al.* in supporting this third hypothesis predicating ventricular "strain."

According to Pardee[11] (p. 14), the QRS is inscribed "while the contraction is spreading throughout the ventricular muscle" (excitation). In Macleod's[7] "Physiology" (p. 284) one reads: "The electrical changes generated within this bundle (His) are not detectable in the E.C.G. but the gradual spread of activity through the powerful ventricular muscle, which is thereby induced, gives rise to the complex series of waves comprising the QRS group."

Resnick,[12a] studying the effect of anoxemia in A–V conduction, found that conduction was first stimulated and then slowed. The effect of anoxemia on conduction varied with severity, duration, the general condition of the animal, its heart rate, and was thought to be due to a "direct effect on the muscle." In another paper[12b] on the effect of anoxia on intraventricular conduction, he found that at first the QRS interval shortened but later lengthened. He concludes that "ventricular aberration in clinical cases is an indication of more or less serious disturbance of the function of the Purkinje tissues."

Bazett and Sands[3] commonly found an increased QRS in dogs with experimental aortic regurgitation.

All these observations tend to show that where the intraventricular pressure is increased (as it is mechanically in aortic regurgitation), or where there is a concomitant anoxemia (which may occur when the intraventricular pressure is considerably raised), there is slowing of intraventricular conduction. (This widening of QRS was regularly obtained in animal experiments.)

Experimental Study. *Methods.* Left heart strain was produced according to a method previously employed by Wiggers[16] (see also Katz, Ralli and Cheer,[5] and Otto[10]). Young dogs or rabbits were put on artificial

respiration and subjected to ligation of several arteries within the thorax (both carotids, the innominate, the left subclavian, and the descending thoracic aorta). In two series of experiments 15 animals were used. Blood pressure was recorded from one carotid through a mercury manometer. The pressure in this small arterial system was still further increased by injecting saline or glucose through the side arm of the recording cannula, thus increasing the pressure against which the heart must empty. The chest incision was not sewed up but after each inspection the parts were drawn together and the animal covered with a blanket to prevent undue cooling of the heart's surface.

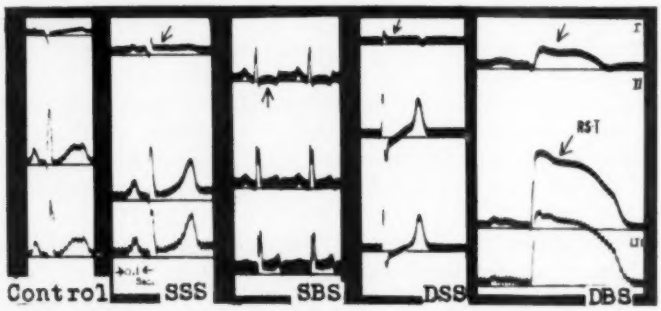

FIG. 1.—Types of muscle bundle lesions sequentially associated with progressive left ventricular strain. Paper speed 50 mm. per second. Standardization: 1 cm. = 1 mv. SSS = superficial sinospiral type of tracing (RS–T = + + +). SBS = superficial bulbospiral type (RS–T = – + +). DSS = deep sinospiral type (RS–T = + – –). DBS = deep bulbospiral, a terminal lesion (RS–T = + +, + +, + +).

Results. It was found that the amplitude (especially of R in Lead 1) increased as soon as the pressure was raised by tying the descending aorta (no veins were tied). The earliest physical change noted was a tendency for the heart to become longer and narrower (pericardium closed). With continuing moderately high pressure or with sudden increase of pressure, the S–T segment in all leads of the electrocardiogram was slightly elevated. This is the characteristic change found in experimental infarction of the superficial sinospiral muscle (see Fig. 1, SSS). When pressures were raised still higher, the amplitude of the pulse pressure increased, and presently $S–T_1$ became depressed, and $S–T_3$ became elevated. This is the characteristic change found in experimental infarction of the superficial bulbospiral muscle (see Fig. 1, SBS). If fluid was rapidly introduced into the arteries and an electrocardiogram taken during the forceful injection, it was noted that T_2 abruptly became negative and that this negativity disappeared and T_2 became as positive as ever when the heart had adjusted to the pressure increase. This T_2 reversal could be carried out many times during an experiment, but eventually the negativity of T_2 tended to become permanent. In one experiment fluid was introduced into the ventricle itself, 80 cc. given very rapidly. The left ventricle dilated and fibrillation resulted (see Fig. 2).

Such experiments indicate the following order of strength of left ventricular muscles, weakest superficial sinospiral, then superficial bulbospiral, deep sinospiral and finally the deep bulbospiral as the strongest. This order one would expect from the relative muscle masses. The cuff (deep bulbospiral) is, of course, not absolutely the heaviest, but it is the thickest and experimentally the most essential to the maintenance of blood pressure.

FIG. 2.—Standardization and symbols as in Figure 1. Following gradual rise of intracardiac pressure sufficient to involve three muscles, during recording of first DBS segment, rapid pressure rise was instituted. Note the development of fibrillation followed by spontaneous recovery to a DBS type of record. A second rapid increase of pressure produced another fibrillation from which there was no recovery.

As pressure of a fluid in a closed cavity is exerted equally in all directions, the internal pressure would be expected to dilate first the weakest part of the left ventricle, the apex, which is enclosed by the thin interlocking portions of the superficial sinospiral and bulbospiral muscles only. Not until pressures were greater would the thicker deep sinospiral and deep bulbospiral muscles dilate, expanding the diameters at the base of the heart.

Previous studies (Mall,[8] MacCallum,[6] Robb and Robb[13]) have shown that under certain conditions there is differential hypertrophy of various ventricular muscles. Presumably the weaker muscles, if under continued strain, would stretch or dilate sooner than the stronger muscles. Such stretching of the superficial sinospiral and

bulbospiral muscles offers an explanation of the common and well-established observation (made both clinically and experimentally) that the outflow tract increases in length previous to expansion of the left ventricle at the base and agrees with Uhlenbruck's[15] statement regarding "enlargement" at the apex (which does not necessarily mean hypertrophy), as the cause of electrocardiographic changes in hypertension.

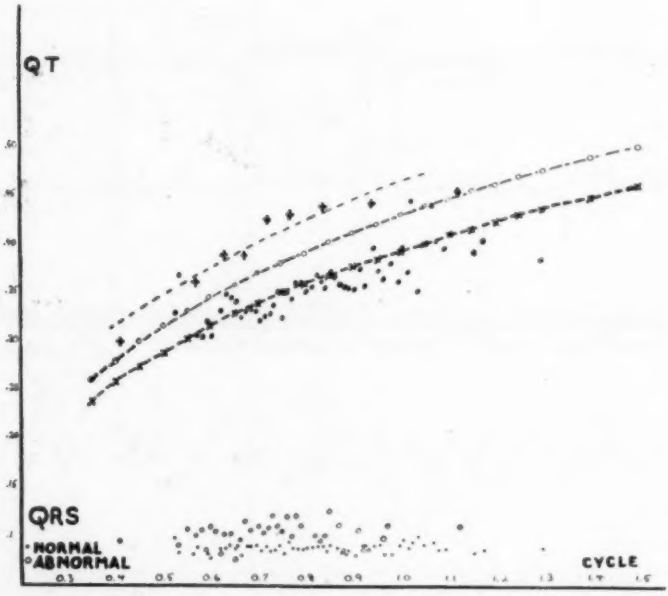

FIG. 3.—Duration of Q–T and QRS plotted against duration of cycle in seconds. Q–T is prolonged in the hypertensives partly due to a longer QRS and partly due to a longer S–T. Q–T: x–x Ashman and Hull's averages for normals; o–o Ashman and Hull's upper limit of normal values; + average data for 100 ambulatory hypertensive patients; *large dots*, average Q–T durations in 300 medical students from this laboratory. QRS: *small dots*, QRS duration in the same 300 medical students; o, average QRS durations in 100 ambulatory hypertensive patients.

In brief, it is demonstrated that the intraventricular pressure can be increased and by gradual increase, strain can be put successively upon the various muscles causing one after another to fatigue. The blood was at all times bright red and did not appear to be deficient in O_2 content. Possibly the alteration in conduction is related to the increased length of conduction pathways (Best and Taylor[4]) occasioned by the tendency of the ventricle to dilate, the effect being to slow conduction along certain pathways and alter the total algebraic summation of all electrical activity.

Clinical Observations. Recently 100 ambulatory hypertensive patients (from Hypertension Clinic of Dr. B. Levinson) have been studied.

Figure 3 presents Q–T and QRS duration plotted against cycle length in these patients. One sees that Q–T duration is definitely increased over that of normals. The values range from 0.3 second when the cycle length is 0.4 second, up to a duration of 0.45 when the cycle length is 1.13 second. QRS duration is also increased in many instances.

S–T changes, when present in clinical hypertension, are comparable to those obtained in acute animal experiments. There were 16 among the 100 whose S–T intervals were isoelectric (16%). Of this group, 75 (75%) showed signs of only superficial muscle strain. There were 37 (37%) who showed a slight elevation of S–T in all leads (superficial sinospiral type of muscle injury) and 38 (38%) others presented depressed S–T_1 and elevated S–T_3, the superficial bulbospiral type of record. Only 9 showed even a mild degree of deep sinospiral alteration (R–T_1 elevated, R–T_3 depressed), which scarcity (9%) is to be expected since none of these patients were decompensated. None showed the deep bulbospiral type of electrocardiogram (maximal elevation of R–T in all leads) which again supports our previous observation that patients with a lesion in this muscle will not be ambulatory and tend to die quickly. Marked deep sinospiral or deep bulbospiral lesions would be expected only during decompensation and immediately before death, hence to see such pictures we require more records taken of patients in extremis.

Discussion. 1. Granting that the electrocardiogram characteristic of hypertension does occur in patients having hypertension and large hearts, it likewise occurs in those with small hearts (also noted by Master,[9] p. 106). Since electrocardiographic signs of hypertension may appear without cardiac enlargement, *size* meaning generalized hypertrophy cannot be the exclusive cause of such signs.

One sees similar electrocardiograms (usually either superficial sinospiral or superficial bulbospiral types) produced under various conditions placing extra demand on the left ventricle, such as aortic stenosis and insufficiency, coarctation of aorta with hypertension, von Gierke's disease; and patent ductus arteriosus with large left ventricle (see Master's Figs. 31 *A* and *I*, 38, 52, 55, 57, respectively). The superficial muscle type is sometimes found in pericarditis where generally the superficial muscles alone are involved (see Master's Fig. 61). When both right and left hearts are enlarged, it is obvious that any muscle type or an admixture of all types could be present (see Master's Figs. 47, 48, 49, 51, 54).

2. Uhlenbruck[15] has suggested that "hypertrophy of the apex" may be the explanation of these electrocardiographic changes. It is certainly true that the outflow tract becomes lengthened early and also the apex tends to become rounded. Injury or "strain" in this region may be a more convincing explanation of electrocardiographic signs. Further evidence concerning this change at the apex is found in an experimental study of aortic regurgitation by

Bazett and Sands.[3] When the aortic cusps were broken, and thus an acute rise in left intraventricular pressure produced, the heart silhouette at once became longer and narrower. In that article Figures 2 and 5 show anterior-posterior and lateral Roentgen rays before and after the operation. Their Figure 7 shows electrocardiograms taken before operation, at 6 weeks after the first operation, and at 11 months after the first and 9 months after the second operation. At 6 weeks, one finds S–T_1 elevated, T_1 negative, T_2 negative, T_3 diphasic, S–$T_{2,3}$ depressed. In the subsequent record, S–T_1 is still elevated, T_1 is flattened, T_2 is diphasic, S–T_3 is still depressed, T_3 is positive. There is no left axis deviation. Thus in a chronic experiment where a mechanical load raising the left intraventricular pressure is allowed to operate for 11 months, a deep sinospiral type of electrocardiogram is obtained. Presumably less regurgitation might have resulted in a superficial sinospiral or a superficial bulbospiral lesion and more in a deep bulbospiral, but with three valves injured at two operations a deep sinospiral type did appear. Schnitker[14] reports 8 cases having coarction of the aorta; half of these showed a deep sinospiral type of tracing.

3. Increased intraventricular pressure not only stretches the component muscle bands of the ventricular wall but also would elongate the conducting pathways (whatever histologic forms these may prove to have. Best and Taylor,[4] as previously quoted, mention simple lengthening of a conduction pathway as a possible explanation of the electrocardiographic change. This elongation may be the mechanism of the increase in QRS duration noted in patients and experimental animals alike where intraventricular pressure is increased (Fig. 3).

Conclusions. 1. Because in acute experiments on young animals no hypertrophy and myocardial damage (in the sense of infarct or connective tissue replacement) is present, one must attribute the various results to change in size of the ventricles dependent upon "strain," that is, increased intraventricular pressure with dilatation (rather than hypertrophy).

2. Such a stretching of the musculature demonstrably alters conduction even to the point of causing ventricular fibrillation.

3. Either development of an injury current within a single muscle band or differential slowing of conduction (including recovery) may be regarded as the essential factor resulting in the characteristic electrocardiograms.

4. These S–T shifts in the electrocardiogram, caused by putting strain upon the individual muscle bundles, are the same as those produced by experimental infarction of the same muscle bundles.

5. Acute centralized systemic hypertension, experimentally induced, initiates a series of electrocardiographic changes reflecting the severity of the disturbance. The left ventricle is enclosed by four muscle masses which give way in sequence: the superficial

sinospiral first, the superficial bulbospiral next, later the deep sinospiral muscle, and in extremis, the deep bulbospiral muscle. Our clinical experience parallels the animal data.

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STUDIES ON THE DISTRIBUTION OF POTENTIAL CONCERNED IN THE FORMATION OF ELECTROCARDIOGRAMS.

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During the past 2 years we have been attempting to study various relations among peripheral differences of electrical potential created by cardiac activity in normals and also in patients with various types of cardiac abnormality.[12] This work has led to the development of concepts which we have been unable to reconcile with the time-honored views of Einthoven[2] regarding the distribution of potential on the body surface. Our observations indicate that

certain definite patterns of variations with time, of differences of potential can be recognized over considerable areas of the body surface by the use of appropriate methods. Some of these patterns obtained between paired areas near the heart undergo decrement as distance of paired areas from the heart increases, but along certain radial lines extending from the heart little alteration in contour of pattern is demonstrable between paired areas. It would seem therefore that the distribution of potential on the body surface from electrical phenomena in the heart is quite different from what Einthoven conceived it to be when he made the series of unverified assumptions which underlie the equilateral triangle hypothesis.

It is remarkable that, as judged from the literature, the equilateral triangle hypothesis receives almost universal acceptance without question as to the validity of the assumptions which underlie it. Gildemeister's[4] demonstration of the electrical properties of tissues, Eyster, Maresh and Krasno's[3] studies of impedance, and Katz'[6] studies of the effects of altering conduction from certain parts of the heart, none of which has been controverted, all seem to be ignored and the superstructure erected upon Einthoven's assumptions grows more and more elaborate.

We have previously shown that differences in potential of ventricular origin between areas in the region about the root of the left arm are, with certain exceptions, much greater than those between corresponding areas on the right side.[12] We proposed that, in the majority of subjects, ventricular potential variations in the left arm are principally, but not entirely responsible for the ventricular pattern of Lead 1.* Furthermore, with certain exceptions, the ventricular contour of Lead 1 was found to resemble that of CR_5, although the amplitude of deflections in the chest lead was usually much greater than in Lead 1. In some cases, the resemblance may be closer between Lead 1 and a CR Lead made to some position in the neighborhood of C_5 (*i. e.*, C_4, C_6 or a position slightly above and to the left of C_5) than between Lead 1 and CR_5 itself. If one moves the chest electrode from C_5 to positions successively nearer the left arm, the deflections diminish in amplitude, although the pattern remains much the same.

These observations, based on studies of approximately 700 cases, suggested that potential variations in the left arm are derived mainly from electrical phenomena in those parts of the ventricles responsible for potential variations in the neighborhood of the C_5 position.

Since these observations were published we have made further studies. It has been found that if an electrode connected with the right arm lead wire is placed on the tip of the right acromial process and an electrode connected with the left arm lead wire is placed at

* This statement does not apply to the auricular waves: in this paper we discuss ventricular effects only.

various positions along a line from the tip of the right shoulder to the C_1 position (the arm being regarded as an electrically intermediate position between the tip of the shoulder and the axilla), the ventricular complexes all show the same general pattern as that of

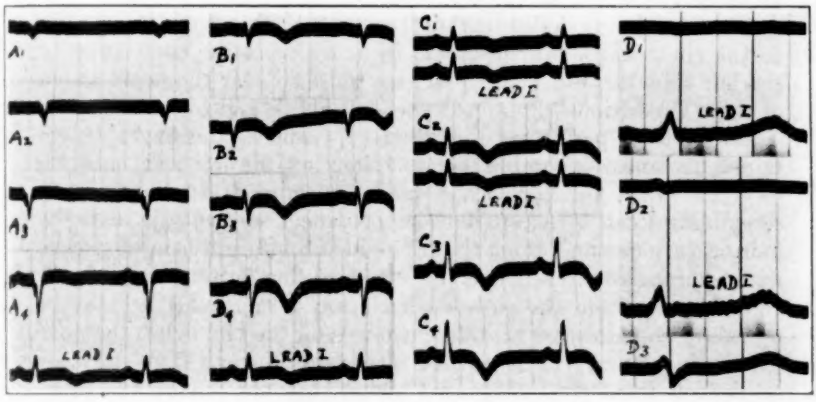

FIG. 1.—In tracings A_1, A_2, A_3, and A_4 the right arm electrode was placed on the tip of the right acromial process. In A_1 the left arm electrode was placed in the right axilla, in A_2 on the right chest just external to the pectoralis muscle, in A_3 approximately half way between the root of the arm and the C_1 position and in A_4 on the C_1 position. Note the similarity in contour of the ventricular complexes and increase in size of deflections as the C_1 position is approached.

In tracings B_1, B_2, B_3, and B_4 the right arm electrode was on the tip of the left acromial process. In B_1 the left arm electrode was placed in the left axilla, in B_2 on the left chest just external to the pectoralis muscle, in B_3 approximately half way between the root of the arm and the C_5 position and in B_4 on the C_5 position. Note the similarity in contour of the ventricular complexes and increase in size of deflections as the C_5 position is approached. The pattern, however, is quite different from that of the right side.

C_1, C_2, C_3, and C_4 are tracings obtained by pairing various areas of the A and B series, using the same polarity as in Lead 1. In C_1 the right and left shoulders were paired, in C_2 the right and left axillæ, in C_3 areas intermediate between the roots of the arms and chest positions, and in C_4 the chest positions C_1 and C_5 were paired. Note the similarity of all these tracings to Lead 1. In some cases, as is pointed out in the text, the close similarity in contour cannot be maintained except by pairing areas at somewhat different levels.

Tracings D_1, D_2, and D_3 were obtained from a different patient. In D_1 (made simultaneously with Lead 1) the electrodes were attached and the connections made as is shown in Figure 2, *A*. The balance of potential on the right side in accordance with the relationship, $P_b - \frac{(P_a + P_c)}{2} \doteq 0$, is shown. In D_2 a similar balance of potentials on the left side is shown. In D_3 the "a" and "c" areas on the left side are paired.

Film speeds in *A*, *B*, and *C*, 25 mm. per second; in *D*, 75 mm. per second.

CR_1 (Fig. 1, A_1, A_2, A_3 and A_4), the deflections becoming successively larger as the left arm electrode is moved to positions successively near the C_1 position (sometimes even as near the ventricles as the C_2 position). A similar study on the left side along a line from the tip of the left shoulder to the C_5 position with the upper and lower

electrodes similarly connected yields tracings similar in pattern to each other (although far different from those obtained from the right side) with gradual increase in amplitude of deflections as the C_5 position is approached (Fig. 1, B_1, B_2, B_3 and B_4). However, in order to obtain the best correlation on the left side, one may have to place the electrodes along a line to the C_4 or C_6 position, the direction probably depending on the size of the heart and its relation to the chest wall. Furthermore, in many cases the correlation on the left side does not hold to an area quite so near the heart as one of these C positions but stops somewhat above and to the left of C_5.

After having performed the above experiments and having ascertained the most favorable line to follow on the left side, and the level to which the correlation holds, a series of tracings closely resembling Lead 1 (except for size of deflections) can be made by pairing various areas along the right-sided line (right arm electrode) with appropriate areas along the left-sided line (left arm electrode). In order to obtain the closest correlation with Lead 1, it may be necessary to pair areas at different levels on the two sides, the positions being found by the method of trial and error. The electrode on the left must often be placed higher than the one on the right. The deflections tend to grow larger as the electrodes are moved to paired areas nearer the C_1 and C_5 positions (Fig. 1, C_1, C_2, C_3 and C_4).

The above studies suggested to us that the changes in potential of ventricular origin in the right arm are derived mainly from electrical phenomena whose sites are in the same parts of the heart as those responsible for the potential changes of the C_1 position, just as the previous studies had suggested that the potential changes of the left arm are derived from electrical phenomena in the same parts of the heart responsible for the potential changes of the C_5 position or some neighboring area. Furthermore, there appeared to be marked decrement in potential variation between the C_1 position and the right shoulder and between the C_5 position and the left shoulder.

If the distribution of potential variations along a line from C_1 to the right shoulder tip and from C_5 to the left shoulder tip (the arm being electrically intermediate between the axilla and shoulder tip) is what we have described it to be, it should be possible to find three positions along either of these lines—"a", a point nearest the C_1 or C_5 position; "c", a point furthest from the C_1 or C_5 position; and "b", a point intermediate between "a" and "c", which would be so related to one another that the difference in potential between area "b", on the one hand, and the mean of the potentials of "a" and "c" on the other, would approximately equal zero for all instants of the ventricular cycle. If we represent potential variation of cardiac origin at any instant of ventricular activity by the letter P, and designate the areas by subscripts, this relationship can be expressed in the following form which can be tested galvanometrically:

$$P_b - \frac{P_a + P_c}{2} = 0$$

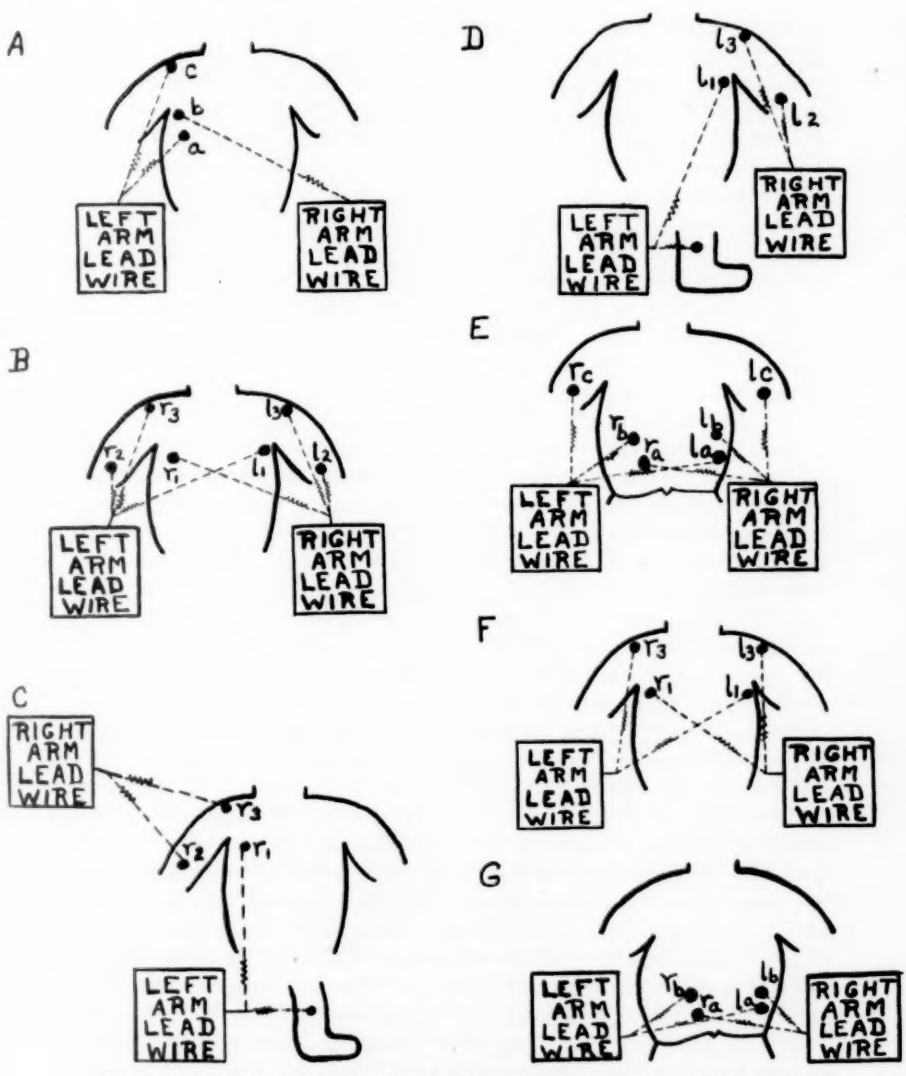

FIG. 2.—*A*, Position of application of electrodes and connections to demonstrate the relationship, $P_b - \frac{(P_a + P_c)}{2} \doteq 0$ (see Fig. 1, D_1 and D_2). *B*, Approximate positions of electrodes and connections used in the test of Equation 4. The r_1 and l_1 positions are found by exploration (see Fig. 3, B_1). *C*, Approximate positions of electrodes and connections used in Equation 6 (see Fig. 3, B_2). *D*, Approximate position of electrodes and connections used in Equation 7 (see Fig. 3, B_3). *E*, Approximate position of electrodes and connections used in the test of Equation 4 in which the C_1 and C_3 positions are included. The r_b and l_b positions are found by exploration (Fig. 3, C_1). *F*, Electrode positions and connections used to reproduce Lead 1 as shown in Equation 8 from positions at some distance from the heart (Fig. 3, B_4). *G*, Electrode positions and connections used to reproduce Lead 1 (Fig. 3, C_4). This relationship is shown by the Equation, $(P'_{la} + P'_{rb}) - (P'_{ra} + P'_{lb}) = P'_{le} - P'_{re}$, which is derived from Equation 4 after substituting the subscripts a, b and e, for 1, 2 and 3 respectively (the principle is the same as that of Equation 8 (Fig. 2, *F*) but in this case the electrode positions are much nearer to the heart.)

Various combinations of positions can be used to show this relationship on either side. Thus on the right side, the tip of the acromial process may be designated area "c", an anterior axillary position area "b", and a position halfway to C_1 tentative area "a". Electrodes are placed on each of these areas and the one on area "b" connected with the right arm lead wire of the electrocardiograph. The wires to electrodes on positions "a" and "c" are interconnected after the interposition of 50,000 ohms resistance* in each, and connected with the left arm lead wire (Fig. 2, *A*). If the lead taken according to these arrangements shows ventricular deflection of any magnitude, the tentative "a" position is not the proper one to satisfy the relationship and this electrode is moved either upward or downward along the line until the smallest possible deflections are obtained. An "a" position can be found in which these are usually less than 1 mm. for the QRS complex (Fig. 1, D_1 and D_2).

Such a result furnishes experimental confirmation for the statement previously made regarding the similarity of patterns of differences of potential along these lines. In dealing with such intricate patterns as QRS complexes it would seem out of the question to assume that the differences of potential could be balanced in this way merely by coincidence. We therefore feel justified in stating that the patterns of differences of potential remain remarkably constant along each of these more or less radial lines from precordium to shoulder tips (although quite different on the two sides), but that decrement in potential variation seems to be considerable as distance from the heart increases. As a matter of fact, it is these characteristics which make possible the balancing of potential differences by this simple procedure.

The above-mentioned relationships offer a new approach to the study of electrocardiography, *i. e.*, by the development of a method for isolating certain patterns of ventricular potential variation which are present on the body surface. We shall assume that potentials of non-cardiac origin can be ignored with safety in electrocardiography. Our standard of reference for variations of potential of cardiac origin is an arbitrarily assumed base line of potential, upon which the cardiac potential is superimposed. It is not essential that this assumed base line of potential be identical for various paired areas, since differences which may be present are neutralized in the process of electrocardiography. It is obviously impossible to measure directly variations of potential of cardiac origin against this arbitrarily assumed constant potential.

The term P which we have used in the relationship

$$P_b - \frac{P_a + P_c}{2} = 0,$$

* An amplifier type electrocardiograph must be used when these high resistances are employed and the room must be shielded from alternating currents.

to designate ventricular potential may be considered to be composed of two possible components with reference to this arbitrarily assumed constant potential. One of these is that part of the potential variation of areas along the radial lines mentioned which is responsible for the pattern of differences of potential recorded between various paired areas situated along each of the lines. This component of the potential which is balanced experimentally may be designated by the term P′ with a subscript to represent the area. However, in addition to this P′ pattern, there is a theoretical possibility of additional potential change in all the areas, which however unlike the P′ pattern is not subject to decrement and is therefore the same in all the areas under consideration. Such potential may be designated "X". The relationship

$$P_b - \frac{P_a + P_c}{2} \doteqdot 0$$

may therefore be expressed as follows:

$$(P'_b + X) - \frac{(P'_a + X) + (P'_c + X)}{2} \doteqdot 0 \quad \text{or} \quad P'_b - \frac{P'_a + P'_c}{2} \doteqdot 0$$

It is obvious from the above that the actual value of the "X" potential does not influence the accuracy of the approximation

$$P'_b - \frac{P'_a + P'_c}{2} \doteqdot 0,$$

since "X" has the same value at any instant in each of the 3 areas.

However, in certain of the relationships to be discussed later in this paper the actual value of the "X" potential, if it exists, becomes a matter of importance. As will be shown by experimental data, there are a number of indications which suggest that it is non-existent. We shall therefore assume provisionally for purposes of clarifying the discussion, that it can be ignored but shall later consider its possible bearing on results.

If three areas could be found with patterns of ventricular potential variation so related that at every instant the potential variation of one area equalled the sum of the potential variations of the other two, one could utilize this relationship to measure the potential variations of a fourth area. Thus, if we represent the ventricular potential for any instant by P′ (as defined above) and if Areas 1, 2 and 3 fulfilled the relationships expressed above, this could be stated:

$$P'_1 = P'_2 + P'_3 \quad \text{or} \quad P'_1 - P'_2 - P'_3 = 0 \quad \text{or} \quad P'_1 - (P'_2 + P'_3) = 0$$

If then we wish to measure the potential variations of the left leg or any other area, we add this expression to both sides of the third equation without changing the equality.

Thus:

$$[P'_1 + P_{\text{left leg}}] - [P'_2 + P'_3] = P_{\text{left leg}}$$

The value for the left side of this equation can be determined galvanometrically if the locations of Positions 1, 2 and 3 are known, and

since, according to the assumption, the values balance each other at every instant of time except for $P_{left\ leg}$, the galvanometer can be made to record the potential variations of the left leg as indicated by the equation.

The attempt to put the above principle into practice led to certain difficulties. Obviously the relationship $P'_1 = P'_2 + P'_3$ cannot be tested galvanometrically, so that one still lacks a method for finding areas with such relationships even if they do exist. However, if two such combinations of areas could be discovered, one on the right and the other on the left, a galvanometric test of balance of cardiac potential variations could be made, although such a test would establish only the correctness of the combined equation and not that of each component part.

Our studies of the peripheral electrical field mentioned above have shown that combinations of three areas can be found, along either of the lines from the right or left chest position to the corresponding shoulder tip, whose relations are such that there is practically no difference of potential between one and the *mean potential* of the other two. We therefore attempted to find combinations of three positions along each line whose relationship is such that the potential variations of one area equals the *sum* of the potential variations of the other two. If, on the right and left sides we designate the three hypothetical positions r_1, r_2, r_3 and l_1, l_2, l_3 respectively, r_1 and l_1 being nearest the heart, r_3 and l_3 farthest away and r_2 and l_2 the intermediate positions, the assumed relationships of their potential of ventricular origin for any instant of time may be expressed as follows:

$$(1)\quad P'_{r_1} - (P'_{r_2} + P'_{r_3}) = 0$$
$$(2)\quad P'_{l_1} - (P'_{l_2} + P'_{l_3}) = 0$$

If Equation 1 be subtracted from Equation 2 one obtains

$$(3)\quad [P'_{l_1} - (P'_{l_2} + P'_{l_3})] - [P'_{r_1} - (P'_{r_2} + P'_{r_3})] = 0$$

By rearrangement of terms

$$(4)\quad [P'_{l_1} + P'_{r_2} + P'_{r_3}] - [P'_{r_1} + P'_{l_2} + P'_{l_3}] = 0$$

In formulating the simple equations stated above we have had to make the assumption not only that the "X" potential is negligible, but that the decrement in ventricular potential in the areas under discussion is such that, as distance from the heart increases, variations of ventricular potential from the arbitrarily assumed base line at the distal end of either line must not be more than half those at the proximal end. Therefore in our first test of Equation 4 it seemed best to choose r_3, r_2, l_3 and l_2 positions far from the heart. Consequently, electrodes were attached to the tips of each shoulder (r_3 and l_3 positions) and to each arm (r_2 and l_2 positions). The attempt was then made to find r_1 and l_1 positions which in conjunction with these other four arbitrarily selected areas would satisfy Equa-

tion 4. A tentative r_1 position is chosen on the chest wall about half way between the attachment of the right arm and the C_1 position, tentative l_1 about half way between the attachment of the left arm and the C_5 position and electrodes are fixed to these two areas. Wires from the electrodes on the three areas designated in the first bracket of Equation 4, after the interposition of 50,000 ohms resistance in each, are interconnected with the left arm lead wire of the galvanometer. Similar connections of the three areas designated in the second bracket of Equation 4 are made with the right arm lead wire (Fig. 2, *B*). The sensitivity of the galvanometer is standardized so that 1 m.v. = 2 cm.* If difference of potential is found to exist between the two groups of areas (*i. e.*, if there is an appreciable string deflection during ventricular systole), Equation 4 is not satisfied. The next step, then, is to find by the process of trial and error the r_1 and l_1 positions which most nearly satisfy the equation. This is done by exploring on the right side until an area is found which yields the smallest deflections with the electrocardiographic connections described above. This area now becomes tentative r_1 and is used in the next procedure which is to explore the left side until an area is found which yields the smallest possible deflections. This area is now designated l_1. The right side is then reëxplored for minor corrections in r_1 position which best satisfy Equation 4 (Fig. 3, B_1).

We have used the above procedure in 23 cases and have been able to balance the potential variations so that with the sensitivity mentioned above, deflections did not exceed 1 mm. at any time during the QRS complex. Ordinary chest electrodes 2.9 cm. in diameter were used. It is possible that if we had used smaller electrodes an even better experimental approximation to the prediction would have been obtained. The r_1 and l_1 positions which yielded the best results for the QRS complexes were not always the identical r_1 and l_1 positions which yielded the best results for the T waves, possibly because of differences in position of the ventricles during these two phases of systole. Having found combinations of areas whose potential variations of ventricular origin balance each other in such a way as to satisfy Equation 4 with a close approximation to accuracy, it is implicit in the results that Equation 3 must also be satisfied. This can be shown in the following way: The ventricular potential of an additional area such as that of the left leg may be added to each bracket without altering the value of the equation. Thus:

$$(5)\quad [(P_{\text{left leg}} + P'_{l_1}) - (P'_{l_2} + P'_{l_3})] - [(P_{\text{left leg}} + P'_{r_1}) - (P'_{r_2} + P'_{r_3})] = 0$$

The values for each of these brackets can be obtained galvanometrically. Thus, in the case of the first bracket, electrodes are

* The electrocardiogram resulting from this standardization requires a correction by the factor 1.5. The standardization of 1 m.v. = 3 cm. was not used for technical reasons.

applied on the designated areas and each connected with a wire in which 50,000 ohms resistance is interposed. Beyond the resistances, the wires to electrode positions designated in the first parenthesis are interconnected with the left arm lead wire. Those in the second parenthesis, after the interposition in each of 50,000 ohms of resistance, are similarly interconnected with the right arm lead wire. The galvanometer is carefully standardized so that 1 m.v. = 2 cm. and a tracing made (Fig. 2, *D*). A similar procedure is then carried out in the case of the positions designated in the second bracket (Fig. 2, *C*). In all cases in which Equation 4 had been satisfied, the patterns of ventricular deflections obtained by these two procedures are with one exception* quite similar (Fig. 3, B_2 and B_3).

LEGEND FOR FIG. 3.

FIG. 3.—Tracings obtained from a patient several days after the development of acute posterior infarction. In the left column conventional leads are shown made with a film speed of 25 mm. per second. B_1 represents the balance of potentials obtained by the method of Equation 4 using positions far from the heart (see Fig. 2, *B*, for diagram of connections). C_1 represents the balance of potentials obtained by the method of Equation 4 including positions near the heart (see Fig. 2, *E*). B_2 represents the "left leg potential" obtained by the method of Equation 6 (see Fig. 2, *C*). B_3 represents the "left leg potential" obtained by the method of Equation 7 (Fig. 2, *D*). C_2 represents the "left leg potential" obtained by the method of Equation 6, using positions near the heart as shown in Figure 2, *E* (in this instance, the C_1 position is used as one of the areas for balancing the C_1 pattern of potential). C_3 represents the "left leg potential" obtained by the method of Equation 7, using positions near the heart as shown in Figure 2, *E* (in this instance a position slightly above the C_4 position is used as one of the areas for balancing the "C_5 pattern" of potential). B_4 is the tracing obtained using the areas and connections indicated by the left side of Equation 8 (Fig. 2, *F*) taken simultaneously with a tracing made according to the connections indicated in the right side of Equation 8 (which is Lead 1). C_4 is the tracing obtained using the areas and connections indicated in the left side of the equation stated in the legend of Figure 2, *G*, taken simultaneously with a tracing made according to the connections indicated in the right side of that equation (which is Lead 1). B_5 represents $r_1 - r_2$ (Fig. 2, *F*). C_5 represents $r_a - r_b$ (Fig. 2, *G*). B_6 represents $l_1 - l_2$ (Fig. 2, *F*). C_6 represents $l_a - l_b$ (Fig. 2, *G*). B_7 represents "right arm potential" obtained by the method of Equation 6, using positions distant from the heart (but analogous to method shown in Figure 2, *C*). C_7 represents "right arm potential" obtained by the method of Equation 6 in which the C_1 position was one of the areas used (*i. e.*, from positions near the heart). B_8 represents "left arm potential" obtained by the method of Equation 6, using positions distant from the heart. C_8 represents "left arm potential" obtained by the method of Equation 6 in which the C_1 position was one of the areas used.

According to the relationships stated in the text, B_5, B_7, C_5 and C_7 should be practically identical. All show very small deflections. However, very slight discrepancy or technical error may distort the pattern when the deflections are small as in the case of C_5 and to a lesser extent C_7. B_2, B_3, C_2 and C_3 should be identical. In this group the pattern is well maintained because of larger deflections, despite the differences in the procedures by which the tracings were obtained. B_4 and C_4 should be practically identical and B_6, B_8, C_6 and C_8 should also be practically identical. The patterns are well maintained in both groups; the discrepancies in size of deflections could have been corrected by slight readjustments in positions of electrodes.

* When the deflections obtained by these procedures are extremely small the combination of technical error (which may be considerable in any one of a long series of experiments, each rather complex) plus admitted slight discrepancy between theory and experimental findings, is sometimes great enough so that similarity of pattern cannot be demonstrated. (See Fig. 3, B_5 and C_5, B_7 and C_7.) Such discrepancies are to be expected in dealing with areas of very slight potential variation.

It is obvious from these relationships that Equations 1 and 2 are approximately correct and the "X" potential negligible or each contains a similar error due to similar values of "X" potential in each. If they are correct, the two galvanometric procedures just described actually record the potential variations of the left leg.

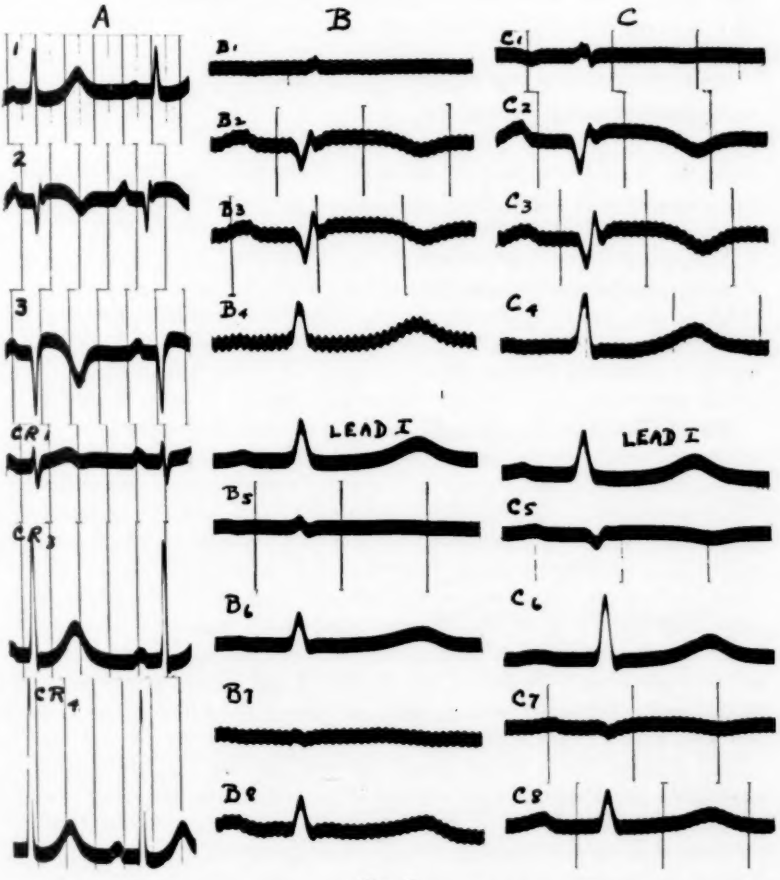

FIG. 3

This can be shown mathematically by adding $P_{\text{left leg}}$ to both sides of Equations 1 and 2. Thus:

$$(6)\quad (P_{\text{left leg}} + P'_{r_1}) - (P'_{r_2} + P'_{r_3}) = P_{\text{left leg}}$$

and

$$(7)\quad (P_{\text{left leg}} + P'_{l_1}) - (P'_{l_2} + P'_{l_3}) = P_{\text{left leg}}$$

Another relationship implicit in the satisfaction of Equation 4 is shown by transposition of terms. Thus from Equation 4 the following is derived:

$$(8)\quad (P'_{l_1} + P'_{r_3}) - (P'_{r_1} + P'_{r_2}) = P'_{l_1} - P'_{r_2}$$

The value of $P'_{l_2} - P'_{r_2}$ is obviously that of Lead 1, since the l_2 area is the left arm and the r_2 area is the right arm. This relationship can be tested by taking an electrocardiogram after disconnecting the right and left arm electrodes from the connections used in the test of Equation 4 (Fig. 2, *F*). It is found that, despite the fact that none of the four electrodes indicated in the left side of Equation 8 is on either arm, the result obtained is practically identical with Lead 1 (Fig. 3, B_4).

From Equation 8 the following is obtained by rearrangement of terms:

$$(9) \quad (P'_{l_1} - P'_{l_3}) - (P'_{r_1} - P'_{r_3}) = (P'_{l_2} - P'_{r_2}).$$

Equation 9 can be tested by recording the differences of potential of the areas in each parenthesis on the left side of the equation simultaneously with Lead 1 (areas but not connections shown in Fig. 2, *F*). If Equations 1 and 2 are correct, $P'_{l_1} - P'_{l_3}$ (Fig. 3, B_6) must represent the ventricular potential variations of the left arm and $P'_{r_1} - P'_{r_3}$ (Fig. 3, B_5) must represent the ventricular potential variations of the right arm. Practically identical patterns of potential variation are also obtained for the right arm and for the left arm by the use of the procedures indicated in Equations 6 and 7 (Fig. 3, B_7 and B_8).

These studies obviously add further evidence to support the view expressed earlier in the paper concerning the formation of the traditional Lead 1 of the electrocardiogram irrespective of the value of "X" potential. Thus Lead 1 is formed by: (1) the pattern of potential variation of a chest position just outside the C_5 position which has undergone great decrement at a position so far away electrically from the heart as the left arm, minus (2) the pattern of potential variation of the C_1 position which has also undergone great decrement at a position so far away electrically from the heart as the right arm. However, the results of our former study showed that usually (although not always) it is the potential pattern of the left arm which dominates Lead 1.[12]

Our studies, however, have not proven that the "X" potential is negligible nor that we have succeeded in recording the ventricular potential variations of a single area. It is conceivable that a pattern of potential common to all six of the areas r_1, r_2, r_3, l_1, l_2 and l_3 may be present, which is not subject to the decrement of the C_1 and C_5 patterns of potential and is therefore not recognized. If this were the case such a pattern could not be recognized by the procedures used in this study and would therefore introduce a constant error in our attempts to measure the potential variations of a single area. Thus, it might be argued that when we utilize Equations 6 and 7 to measure the potential variations of the left leg, we may have balanced out of the equation the potential variations of the type subject to decrement in the "r" positions and in the "l" positions, but not the "X" potential variation. The latter would have to be transmitted from electrical charges in some part of the heart in con-

tact with a good conductor such as muscle, so that no important differences in this pattern of potential would exist among any of the six areas. If this were the case, a part (or possibly most) of the potential variation which we ascribe to the leg would actually be derived from the upper part of the body.*

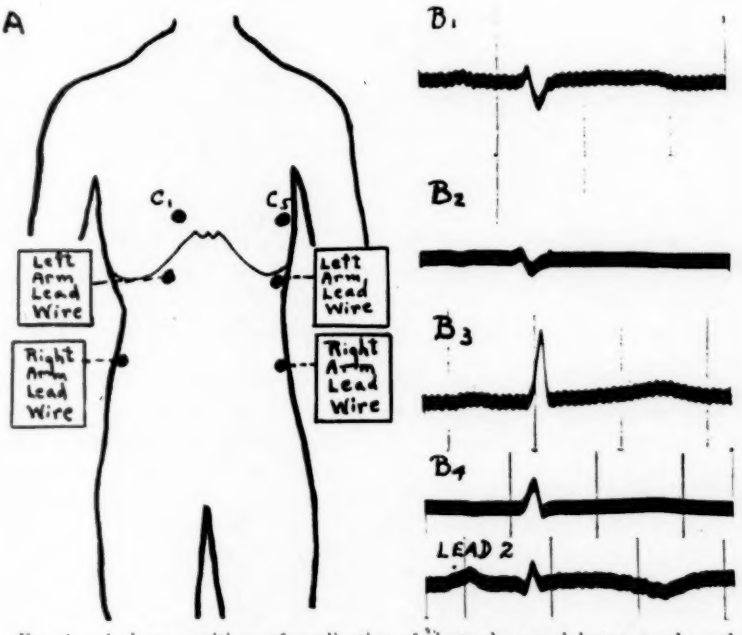

FIG. 4.—*A* shows positions of application of electrodes on abdomen to show the presence of the C_1 and C_5 patterns of potential below the level of the diaphragm. B_1 shows the C_1 pattern of potential recorded by the method of Equation 6. B_2 is obtained by pairing the areas on the right side of the abdomen as shown in Diagram A. Note the resemblance of ventricular patterns. B_3 is the C_5 pattern of potential obtained by the method of Equation 6. B_4 was obtained by pairing the areas on the left side of the abdomen as shown in Diagram A. Note the resemblance of ventricular patterns except for a small S wave in B_4. (Film speed in all tracings 75 mm. per second.)

Some preliminary studies of the part of the electrical field below the diaphragm have convinced us that the distribution of at least three different patterns of potential variation can be recognized in that part of the body. For such a demonstration a patient is selected who presents the typical electrocardiogram of posterior infarction so that leads from each upper extremity to parts of the body below the diaphragm present certain identifiable common characteristics. If a tracing is made with the left arm lead wire

* If "X" potential is not ignored, Equation 6 must be written as follows:

$$(P_{\text{left leg}} + P'_{r_1} + X) - (P'_{r_2} + X + P'_{r_3} + X) = P_{\text{left leg}} - X$$

electrode on the upper abdomen below the C_1 position and the right arm lead wire electrode on the lower part of the right flank, a tracing can be obtained in which the deflections are very small but in which the similarity in contour to those obtained along the line from C_1 to the top of the right shoulder can be recognized (Fig. 4, *A*, B_1 and B_2). This seems to mean that the C_1 pattern of potential is rather feebly distributed over the right side of the abdomen with decrement as distance from the heart increases. If a similar lead is made from the left upper abdomen below the C_5 position to the left flank, the similarity in contour to the leads made along the line from C_5 to the top of the left shoulder can also be recognized (Fig. 4, *A*, B_3 and B_4). This appears to mean that the C_5 pattern of potential is also rather feebly distributed down the left side of the abdomen with decrement as distance from the heart increases. These phenomena, however, are apt to be overlooked in tracings between the right arm and various lower parts of the body, even in cases with posterior infarction, since the pattern is dominated by the potential variations presumably derived from the area of injury and subject to little decrement on the body surface below the diaphragm (Fig. 4, Lead 2).

In view of the apparent variability in decrement of the various component units which make up the potential variations of areas in the lower part of the body, we attempted to test Equation 4 by including positions as near to the heart as possible, in order to obtain information as to whether this state of affairs might exist in the upper part of the body. Our previous findings indicated that it should be possible to satisfy Equation 4, using such positions, provided decrement in potential variation between the chest and arm positions on each side is sufficiently great. Furthermore, if Equation 4 could be satisfied using positions, some of which are near the heart, and if identical results could be obtained in Equations 6 and 7, we should have to conclude that either Equations 1 and 2 are correct, or the "X" potential variation, not reflected in the previous studies (because it was identical at the six positions previously used), is also present and of the same size at areas so near the heart as the C_1 and C_5 positions. In order to avoid confusion in terminology when using areas near the heart, the three areas on the right side are designated r_a, r_b and r_c, and the three areas on the left side, l_a, l_b and l_c, r_a and l_a being the areas nearest the heart, r_b and l_b the intermediate areas, and r_c and l_c the areas furthest from the heart. Thus, in the series of equations which have been formulated r_a and l_a can be substituted for r_1 and l_1; r_b and l_b for r_2 and l_2; and r_c and l_c for r_3 and l_3 respectively. Electrodes were placed on the arms (in this instance areas r_c and l_c), on the C_1 and C_5 positions (in this instance areas r_a and l_a) and on intermediate positions between the attachments of the arms and the C positions (tentative areas r_b and l_b). The method used was that described previously

except that the intermediately placed electrodes were used to explore (Fig. 2, *E*). The approximate satisfaction of Equation 4 is technically much more difficult when these positions are used than when all the electrodes are placed a considerable distance away from the heart. The sources of difficulty we have encountered have been as follows: On the right side, difficulties all seem to have to do with decrement in potential variations between the C_1 position and the right arm. Thus, in many cases, the potential variations of the right arm seem to be practically negligible and under these circumstances the r_b position is found to be so close to the r_a (C_1) position that the electrodes could not be placed on these two positions without touching each other. In others, potential variations of the right arm may be greater than half those of the C_1 position so that no intermediate point will satisfy the equation. Under these circumstances, the equation can occasionally be satisfied by moving the electrode from an intermediate position to the top of the right shoulder. On the left side, similar difficulties may be encountered because of rate of decrement in potential variations, but in addition, the direction of the line extending downward and inward from the shoulder, along which electrodes can be placed to satisfy the equation, becomes a matter of importance. This line usually extends down to a position just outside the cardiac apex. Occasionally the equation cannot be satisfied by having the l_a position at the level of C_5 but can be satisfied by placing it a few centimeters higher. Another source of difficulty is the relatively great potential variation at positions so near the heart, so that moving an electrode only a few millimeters may make considerable difference in results. However, even with all these difficulties, a reasonably close approximation to Equation 4 can be obtained by using positions near the heart as well as by using positions further from the heart.

Having satisfied Equation 4, with positions near the heart (Fig. 3, C_1), the various other procedures mentioned previously, which are implicit in this relationship, can be carried out with similar results. Thus, after finding the areas which satisfy Equation 4 (Fig. 2, *E*), we obtain, by disconnecting the electrodes attached to the arms (Fig. 2, *G*), a tracing resembling Lead 1 (Fig. 3, C_4) despite the fact that the four positions used in making the tracing may be quite distant from either arm, and at least 2 of them very close to the heart.

The results of the procedures indicated by Equations 6 and 7 for the determination of "potential variations of a single area" are found to be practically the same when the above combinations of areas are used, as in the case of combinations of areas all of which were further away from the heart (Fig. 3, C_2 and C_3). Since in this test the arms are designated areas r_c and l_c, we rearrange terms of Equation 9 (using the appropriate subscripts for this combination of areas) thus:

$$(10) \quad (P'_{la} - P'_{lb}) - (P'_{ra} - P'_{rb}) = P'_{lc} - P'_{rc}$$

In this instance $P'_{lc} - P'_{rc}$ represents the difference in potential between the left and right arms, *i. e.*, Lead 1. The value of $P'_{la} - P'_{lb}$ (Figs. 2, *G*, and 3, C_6) is found galvanometrically to be similar to that of $P'_{l_1} - P'_{l_5}$ (Figs. 2, *F*, and 3, B_6) of Equation 9 despite the marked differences in position of the areas. Likewise $P'_{ra} - P'_{rb}$ (Figs. 2, *G*, and 3, C_5) is found to be similar to $P'_{r_1} - P'_{r_2}$ (Figs. 2, *F*, and 3, B_5).*

Discussion. The demonstration, (1) that certain patterns of ventricular potential variation are present throughout certain body surface areas located along more or less radial lines from the precordium to the shoulder tip, (2) that they are subject to decrement as distance from the heart increases, thus permitting a balance of the potential variations of one position within a given area (with approximate accuracy) against those of two other positions within the same area, and 3, that there are certain other phenomena which depend on these relationships, indicates the advisability of reëxamining prevailing concepts regarding the distribution of potential of cardiac origin on the body surface.

In a system so complex as the human body, composed of many different tissues (membranes, muscle sheets and muscle bundles, bone, fat, lungs, digestive tract and skin), with their different electrical properties, it would seem difficult to justify continued adherence to simplifying assumptions which ignore this state of affairs. A sounder course of procedure would have been an attempt to establish the possible limits of error of such assumptions. If they are as untenable as our experimental work suggests, the subject of cardiac potential distribution at body surface areas some distance from the heart requires reinvestigation.

When electrograms are made with one electrode directly on heart muscle or separated from it only by the thin layer of epicardium, the fundamentally important work of Lewis[7,8] indicates that the major wave of negativity, or the so-called intrinsic deflection of the QRS complex, is due to the arrival of the excitatory process in the subepicardial muscle directly under the electrode. The pre-intrinsic deflection which is positive is derived, according to Lewis, from some deep lying mass of muscle tissue. Lewis showed that the pre-intrinsic deflections begin all over the ventricular surface at nearly the same time, and that the time at which they are recorded over the right ventricle is not disturbed even after transection of the right bundle branch (although the arrival of the intrinsic deflection is delayed by this procedure). He concluded therefore that pre-intrinsic deflections recorded from an electrode over the right ventricle may represent the passage of an excitation wave through portions of the left ventricle. Furthermore, Lewis' experiments showed that, when the positive pre-intrinsic deflections were recorded at the epicardium, negativity was present in an electrode placed on

* Such discrepancies as are present are due chiefly to technical errors.

the endocardium. Wilson[10] who has also performed experiments bearing on this subject has found, in agreement with Lewis' endocardial leads, that the potential of the ventricular cavity with reference to any area distant from the heart falls at the beginning of the QRS complex. Thus it would appear to be clearly established that negativity in deeper layers of the myocardium with reference to the potential of a point distant from the heart may occur at the same time as positivity of the epicardium with reference to the same point. This phenomenon, which is undoubtedly one of major importance in electrocardiography, for which various explanations have been proposed which need not concern us here, is an indication of the complexity of the problem of potential distribution.

When the electrode is moved from the heart to the chest wall directly overlying the heart, the factors determining potential variation have somewhat different relative importance despite the fact that, when the heart muscle is healthy, the QRS pattern resembles that of the epicardial electrogram with pre-intrinsic, intrinsic and post-intrinsic deflections, and the T wave remains upright. In the first place, electrical activity of any kind within the heart may be expected to produce much less effect on the chest walls than on the epicardium. In the second place, it is probable that the effect upon the epicardial electrode is that produced in a small volume of the heart near the electrode. The potential difference between a precordial electrode and some other (skin) electrode is on the other hand most probably determined by electrical phenomena in a volume of the heart considerably larger than that which contributes most to the corresponding potential difference for an epicardial electrode. Thus, when two chest leads are made from positions directly over the ventricle, it seems useful to assume that the potential difference between them is determined in large part by electrical phenomena within certain volumes of the heart. The effect of a particular small volume of the heart upon the difference of potential between the electrodes will depend upon many factors: A, The areas of the skin covered by the electrodes. B, The distances of the particular volume from the electrodes. C, The orientation of muscle fibers in which the phenomena arise, with respect to the electrodes. D, The electrical properties of the intervening tissues.

Everyone who has had experience with multiple chest leads knows that change in the pattern may occur as the exploring chest electrode is moved from one position to another near by. Furthermore, when a lesion is present in the anterior wall of the left ventricle and is reflected by a pathologic pattern of potential variation, maximum at a certain area on the precordium, the pattern in adjacent areas is probably also influenced by the lesion. However, at some distance from the precordial region of maximum abnormality, the electrical effects derived from a part of the ventricle with a normal

architecture may so overshadow the effects from the abnormal region that the pattern of potential variation becomes of the normal type. This does not necessarily mean that no effect is being registered from the area of the lesion, but merely that the effect is not great enough to produce a pathologic pattern.

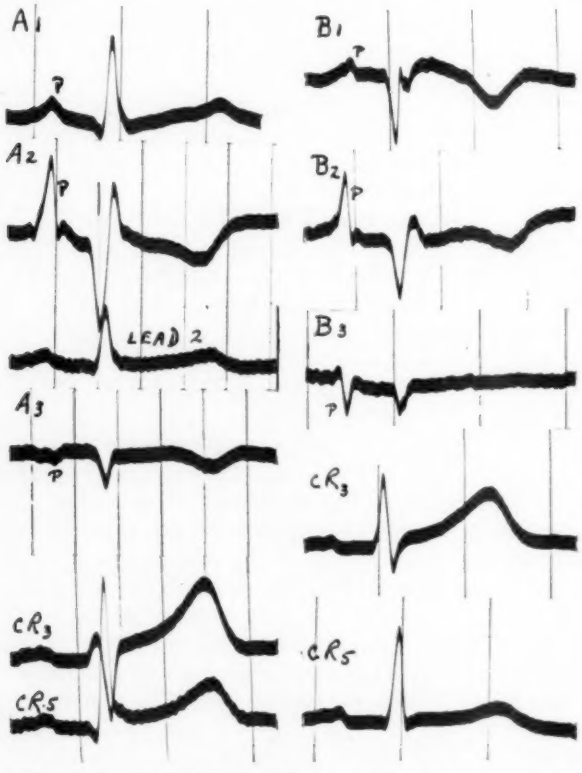

FIG. 5.—The tracings in the left column were obtained from a presumably normal control. A_1, A_2 and A_3 are esophageal leads in which the esophageal electrode is connected with the left arm lead wire and paired with the right arm electrode on the right arm. In A_1 the esophageal electrode was below the auricular level. Note the similarity of the ventricular deflections to those of Leads 2 and CR_5. In A_2 the esophageal electrode was pulled upward about 3 cm. to the auricular level. Note the large P wave and the reversal of ventricular pattern to the so-called endocardial type. In A_3 the electrode has been pulled upward about 3 cm. above the auricular level.

The tracings in the right column were obtained from a patient in the healed stage of posterior infarction. B_1, B_2 and B_3 were made with the esophageal electrode in positions similar to those of A_1, A_2 and A_3, respectively. Note that there is a marked difference in ventricular pattern from that of the healthy heart below the auricular level but not at the auricular level. (Film speed, 75 mm. per second.)

The normal pattern of potential variation in the lower esophagus seems to be much like that recorded from the anterior chest wall (Fig. 5, A_1 and CR_5). However, as the esophageal electrode is

moved gradually upward there may be a startling reversal of pattern with an initial large wave of negativity in the QRS complex and an inverted T wave (Fig. 5, A_2), much like the pattern found anteriorly over an area of infarction. In view of the type of endocardial pattern found by Lewis[7,8] one might raise the question, as Brown[1] has done, whether an electrode lying in the neighborhood of the auricles (or even higher in the esophagus) may not tap the endocardial potential more than that of the epicardium. The importance of this esophageal pattern on the ventricular potential of various body surface areas cannot be evaluated at this time but it might be considerable in certain areas.

While there is a constantly changing contour in the pattern of potential variation as an exploring chest electrode is moved from one position to another directly over the ventricles, the contour over certain other parts of the chest, as has been demonstrated in this paper, does not change materially. Thus from chest positions not directly overlying the ventricles but not far away, patterns of potential variation are obtained on each side, which as we have shown, remain practically constant (subject only to decrement as distance from the heart increases) along radial lines extending as far away from the heart as the tip of each shoulder. We have no satisfactory explanation for these observations. Obviously the body is not functioning with reference to these areas as a homogeneous fluid conductor surrounding the heart. One is reminded of the interesting suggestion of Eyster, Maresh and Krasno[3] that certain tissues (possibly in this case the lungs) may function as "leaky electrostatic condensers" for certain parts of the heart in close relationship with them.

Since our studies have shown that Lead 1 represents the result of subtracting the C_1 pattern of potential (derived chiefly from one part of the heart), from the C_5 pattern* (derived chiefly from another part of the heart) after each has undergone the decrement between its C position and the corresponding arm, the rather dubious scientific standing of Lead 1 becomes apparent. The possible advantages of studying separately the C_1 and C_5 patterns rather than Lead 1 are obvious. Adherents to Einthoven's views must necessarily think that Lead 1 is extremely important. However, since we have shown that the potential patterns which are subtracted from one another to produce Lead 1 are derived mainly from different parts of the heart, it would appear that the contour of the deflections of Lead 1 should have less significance than those of the C_1 and C_5 patterns considered separately. Another objection to Lead 1 is the fact that its contour is affected by certain factors which have nothing to do with the arrangement and magnitude of the electrical

* The term "C_5 pattern" is used for convenience. We have pointed out that in certain cases some neighboring position on the precordium may be the area which gives a pattern corresponding more closely to that of the left arm.

disturbances in the heart itself, *i. e.*, such factors as the electrical properties of the pathways between certain parts of the heart and the arms.* Thus far, we have not found additional advantage to be gained from Lead 1, yet the question may deserve further study.

Differences of potential between electrodes one of which is placed on the lower part of the body seem even more difficult to analyze than those obtained from two electrodes placed on upper parts of the body. It will require many more observations than have as yet been made, before they are well understood. We have shown that the C_1 and C_5 patterns can be demonstrated on certain parts of the abdomen and it is therefore probable that these (and possibly other anterior chest patterns) have some influence upon the potential variations of the legs. However, in a variety of electrocardiographic abnormalities, but especially in so-called posterior infarction, the altered electrical phenomena due to cardiac damage often appear to have an important influence on the potential variations of the lower part of the body surface and little observable influence above the diaphragm. In patients with posterior infarction, leads made between various paired areas both of which are above the diaphragm (such as Lead 1 or even a lead between C_5 and C_1) are apt to show little or no change from the normal; whereas in anterior infarction, leads from paired areas above the diaphragm often show marked abnormalities. However, when one electrode is placed below the level of the diaphragm, in a patient with posterior infarction, a pathologic pattern may be obtained.

It is obvious that the pathologic pattern of potential in posterior infarction must be derived from the changes in electrical activity produced by the lesion. The nearest fixed point to such a lesion where an electrode can be placed in a patient is in the lower end of the esophagus. Various workers[5] have observed that when one electrode is placed in the lower esophagus, tracings can be obtained in cases of posterior infarction which show a definitely pathologic pattern. We have confirmed this observation (unpublished studies) and have studied the esophageal pattern by the methods of Equations 6 and 7 in 2 cases of healed posterior infarction. As compared with normals, initial negativity of the electrode in the lower esophagus during the QRS complex is apt to be greatly increased, its duration lengthened and the succeeding wave of positivity does not rise nearly so far above the isoelectric line (Fig. 5, B_1). Likewise there is negativity of the esophageal electrode during the inscription of the T wave.† These pathologic potential variations are much greater than any which can be obtained from the body surface in such cases.

At the present time one can merely speculate as to the major

* The importance of pathways within the chest can be demonstrated in patients with temporary pneumothorax or hydrothorax.

† The position of the electrode must be determined under fluoroscopic control in order to be certain that it is low in the esophagus. As stated above, in positions only a few centimeters higher, normals may show a similar pattern (Fig. 5, A_2).

source of ventricular potential on the lower part of the body surface. With the limited data in our possession we are inclined to the view that the part of the heart responsible for potential variation in the lower end of the esophagus is likewise responsible for an important part of the potential variation of the lower part of the body. Certainly the changes in lower esophageal leads and in leads made to positions below the diaphragm when posterior infarction is present, would support such a view. However, there is as yet no method for separating the "esophageal" pattern from the other patterns such as the C_1 and C_5 types in the lower part of the body, since we are unable to quantitate the values of the anterior chest patterns in these regions.

At least two attempts to register the potential variations of a single area have been recorded in the literature. The method of Wilson,[11] as is stated by the author, requires an assumption of the validity of the equilateral triangle hypothesis which our work, as well as that of Eyster[3] and Katz[6] has shown to be untenable. The immersion method of Molz[9] requires the untested assumption that the potential of a salt solution bath in contact with the external body surface remains constant throughout cardiac contraction. In view of, (1) the structure of the body with surfaces in the lungs and gastro-intestinal tract which cannot be brought into contact with the salt solution, and (2) the different electrical properties of the various tissues, it would be naive to adopt such an assumption merely because it might hold in case of a technically perfect experiment dealing with homogeneous material of such nature that differences of potential between points could develop only on the surface which is in contact with the salt solution.

We have pointed out above that, provided an assumption is made, Equations 6 and 7 may be used to record the potential variations of a single area with approximate accuracy. This assumption is that no hidden pattern of potential variation is present in the various areas which were used as electrode positions in Equation 4. We have shown that if such a hidden pattern is present, it must be practically identical not only at both the C_1 and C_5 positions but at all other positions along each of the lines extending from C_1 to the tip of the right shoulder, and from C_5 to the left shoulder. Its distribution would therefore have to be through excellent conductors and entirely different from that of the C_1 and C_5 types of potential. This would seem to us to mean that this hypothetical "X" potential would have to arise from other parts of the heart than those from which the C_1 and C_5 patterns are derived. We do not, however, make the assumption that "X" potential is negligible even though there is reason to believe that such is the case.

Finally, it might be worthwhile to try to evaluate the new methods described in this paper. If there is no "X" potential, and if, therefore, we are able to measure, by means of Equations 6 and 7, the

potential variations of any given area on the body surface, the clarification of electrocardiographic conceptions which would result is obvious. Any given lead could be broken down into its two major components, which heretofore have been fused together indistinguishably. However, even if there is an "X" potential, some simplification may be attained. The principle may be discussed by taking Lead 2 as an example. For our present purposes, this lead may be considered as made up of three groups of potentials: (a) the "X" potential; (b) the C_1 pattern which has undergone decrement at a position so far away from the heart electrically as the right arm; and, (c) the potential variations of the left leg. By means of Equations 6 and 7, one group of variables, b, can be eliminated, and the tracing obtained will consist of only two groups of variables instead of three. Thus, if one desires to study the potential variations of the left leg, he can do it more accurately by means of Equations 6 and 7, than by means of Lead 2. So far as we are aware, this represents the first attempt to eliminate variables from electrocardiographic tracings which has not depended upon assumptions of questionable validity.

Summary. 1. Electrocardiograms made between small areas situated along a line drawn from the C_1 position to the tip of the right acromion (the right arm being regarded as an electrically intermediate position between the tip of the acromion and the axilla) all show a ventricular contour similar to Lead CR_1, provided the same polarity is used in all these leads as in CR_1. This we have called the C_1 pattern of potential. The size of the deflections seems to be related to: (1) the potential variations at the C_1 position; (2) the distance of the paired areas from the heart; and, (3) their distance from each other.

2. Electrocardiograms made between small areas situated along a line drawn from a position slightly outside the cardiac apex to the tip of the left acromion (the left arm being regarded as an electrically intermediate position between the tip of the acromion and the axilla) all show a ventricular contour similar to that of the CL Lead made to the position just outside the cardiac apex, provided the same polarity is used in all these leads as in the CL Lead. This we have called the C_5 pattern, although it may be derived from the C_4 or C_6 position, depending on the relation of the cardiac apex to the chest wall. The size of the deflections seems to be related to: (1) the potential variations at the C_5 position; (2) the distance of the paired areas from the heart; and, (3) their distance from each other.

3. By pairing appropriate areas along each of these two lines and making electrocardiograms with the same polarity as in Lead 1, a series of tracings closely resembling Lead 1 can be obtained. The deflections become larger as the paired areas approach the C_1 and C_5 positions.

4. Various combinations of three positions can be found along

each of these two lines whose relationships are such that the ventricular potential of the intermediate position is approximately equal at all instants to the *mean* of the ventricular potentials of the proximal and distal positions.

5. The above-mentioned findings suggest that there is marked decrement in the C_1 pattern between the C_1 position and the right shoulder and also marked decrement in the "C_5 pattern" between the position just outside the cardiac apex and the left shoulder. However, there appears to be very little alteration in contour of either pattern along these radial lines from the precordium to shoulder tip.

6. By methods described in the text, combinations of three positions can be found along each of the two lines, whose relationships are such that the *sum* of the ventricular potential of the area nearest to the heart along one line plus that of the two areas further from the heart on the other line is approximately equal at all instants to the *sum* of the potentials of the other three areas. Furthermore, when such positions have been found, the relationships of the three areas on each side are such that the potential of the proximal area minus the sum of the potentials of the two distal areas on one side is approximately equal at all instants to the potential of the proximal area minus the sum of the potentials of the two distal areas on the other side.

7. On the basis of the above-mentioned relationships, the following may be demonstrated:

A. Lead 1 can be reproduced by the application of electrodes to various combinations of four chest positions without electrodes on either arm.

B. Either the C_1 pattern of potential is almost completely responsible for the potential variations of the right arm and the "C_5 pattern" of potential is almost completely responsible for the potential variations of the left arm, or else there is an additional pattern of potential variation common to all these areas which is not reflected in the tracings because it is identical at areas so near the heart as the C_1 and C_5 positions, and so far away as the right arm or tip of the right shoulder and the left arm or the tip of the left shoulder.

C. No matter which of the above alternatives is correct, Lead 1 represents the subtraction of the C_1 pattern of potential variation after it has undergone decrement, from the "C_5 pattern" after it has also undergone decrement.

D. If the first alternative stated above in "B" is correct, a method can be devised for recording the potential variations of ventricular origin in a single area. If the second alternative is correct, the method as described records the potential variations of a single area minus the hypothetical concealed pattern of potential common to all the areas mentioned in "B". Thus, no matter

which alternative is correct, the study of potential patterns can be simplified by the elimination of the obscuring effects of the C_1 and "C_5 patterns" present in upper parts of the body.

8. The presence of the C_1 and "C_5 patterns" of potential can be demonstrated below the diaphragm by appropriate methods. No test was made for other anterior chest patterns. The rather scanty evidence now available, however, indicates that a pattern or patterns of potential which seem to exert comparatively feeble effects above the diaphragm (at least in the formation of the C_1 and C_5 patterns) influence greatly either the potential variation of the lower part of the body or the hypothetical concealed potential not subject to decrement in the upper part of the body. From the practical point of view it would appear to make little difference which of these alternatives is correct.

9. Limited studies of the lower esophageal pattern of potential (below the level at which the electrode is in close contact with auricular muscle) suggest that the part of the heart responsible for this pattern has a marked effect on the form of the ventricular electrocardiogram when an area above the diaphragm (at some distance from the precordium) is paired with an area below the diaphragm.

10. The pattern of esophageal potential, at and above the level where the electrode is in close proximity to auricular muscle, resembles that which has been described as the endocardial pattern of potential variation more closely than it resembles the epicardial pattern. The effects of this pattern are probably not entirely negligible on the body surface.

11. The relationships among potential differences on the body surface resulting from cardiac electrical activity appear to be different from what Einthoven conceived them to be when he formulated the equilateral triangle hypothesis. The demonstration that certain patterns of potential variation found to exist in positions near the heart remain intact in positions far from the heart, except for decrement, and the relationships discovered as a result of these phenomena indicate the necessity for reconstructing electrocardiographic theory. An attempt has been made to begin this reconstruction.

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A CLINICO-PATHOLOGIC CORRELATION BETWEEN HEPATIC DAMAGE AND THE PLASMA PROTHROMBIN CONCENTRATION

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Experimental data[3–5,8–11] indicate that the liver is concerned in the production of prothrombin, and it has been suggested that the concentration of prothrombin in the plasma might be used, under certain circumstances, as a test of hepatic function. In patients suffering from damage to the liver, it has been observed that the concentration of prothrombin is usually diminished, and that it cannot be elevated by the administration of vitamin K.[2,6] In most of the instances reported, the estimation of hepatic damage has been based solely on clinical evidence. In the present investigation, the determination of damage to the liver was ascertained by histopathologic study of material obtained at operation or at autopsy.

The prothrombin concentration was determined by the method of Quick.[7] A concentration of 70% or greater was considered normal, since that value occurred in 98 of 100 normal subjects tested in our laboratory. In all patients with extrahepatic biliary obstruction, the recorded value of the prothrombin concentration was that obtained after the administration of an adequate dose of vitamin K. Details regarding the clinical course and response to vitamin K in many of these patients are recorded in previous communications.[1,2,6]

The material for this report was selected from patients in whom a clinical diagnosis of disease of the liver was made, and some in whom there was no clinical evidence of hepatic damage. Patients in whom

the prothrombin concentrations were obtained within 1 day of death were included in the study because the results of these tests were in all instances consistent with previous determinations made on these same patients. We have not observed in any patient evidences of any specific agonal physiologic alterations in the prothrombin concentration. No case was included in this study where the last prothrombin concentration had been determined more than 30 days before death or operation. A further exclusion was made of all cases in which the clinical course or autopsy findings clearly indicated that the pathologic alterations observed in the liver were initiated or had progressed markedly subsequent to the last determination of the prothrombin concentration. An instance of this type of exclusion is that of the following case of a woman, aged 54, who developed a fulminating postoperative infection (*B. welchii*) of the liver and died within 24 hours; the infection had obviously occurred after the last determination of the prothrombin concentration which had been done on the day before operation.

In the 8 patients observed at the time of operation, a biopsy was taken and detailed notes were recorded of the gross appearance of the liver. In the 34 instances where autopsies were obtained, the gross appearance of the liver was recorded, and sections from many areas were obtained for histopathologic examination. An attempt was made to determine the relationship between the plasma prothrombin concentration and the type and extent of the pathologic processes observed. In each instance the pathologist designated the major histopathologic change, and estimated its severity without a knowledge of the prothrombin concentration.

Our results are given in Table 1. The prothrombin concentration was normal in 20 instances. Of these, 8 had no demonstrable damage to the liver, 3 had slight focal necrosis, 1 had slight passive congestion, 1 had marked fatty infiltration, 3 had cholangeitis, 3 had slight portal cirrhosis, and 1 was diagnosed "hepatoma." In 22 instances the prothrombin concentration was diminished. Of these, 8 had various types of cirrhosis, 6 had primary or metastatic carcinomata, 4 had fatty infiltration, 2 had subacute yellow atrophy, 1 had miliary tuberculosis, and 1 was diagnosed as having "slight leukemic infiltration." In general, the prothrombin concentration was normal when there was little or no destruction of parenchymal tissue, and it was diminished when there was moderate or advanced destruction of parenchymal tissue. There were 2 subjects who deviated markedly from this rule. In 1 subject (Case 35) with extensive destruction of the liver by infiltrating hepatoma, the prothrombin concentration was 70%. In another subject (Case 42) with only slight leukemic infiltration, the prothrombin concentration 2 days before death was 40%. Subsequently a 50 mg. dose of phthiocol administered intravenously was without effect. Three hours before death the prothrombin concentration had dropped to 25%.

TABLE I.—CORRELATION OF PROTHROMBIN CONCENTRATIONS AND HISTOLOGIC CHANGES.

Case No.	Age.	Sex.	Prothrombin concentration. %	Time before autopsy or biopsy (days).	Autopsy, hrs. post-mortem.	Size of liver (gm.).	Histopathologic examination. Diagnosis.	Degree.*
1	67	F	70	4	½	1080	Normal	0
2	65	F	100	1	Biopsy	Normal	Normal	0
3	30	M	100	6	1	1780	Normal	0
4	31	M	90	1	Biopsy	Normal	Normal	0
5	38	F	100	1	Biopsy	Normal	Normal	0
6	58	M	80	4	2	1700	Normal	0
7	30	M	100	6	9	1880	Normal	0
8	69	M	85	4	3½	1460	Normal	0
9	38	F	70	13	2½	1570	Focal necrosis	+
10	63	F	90	1	1	1700	Focal necrosis	+
11	21	F	70	8	10	1170	Focal necrosis	+
12	53	M	70	20	10	1900	Passive cong.	++
13	61	M	65	5	14	1520	Fatty infiltr.	+
14	51	F	55	½	9	2200	Fatty infiltr.	+++
15	28	M	65	6	4	1600	Fatty infiltr.	+
16	50	M	60	4	14½	1600	Fatty infiltr.	+
17	40	F	70	4	6	1240	Fatty infiltr.	+++
18	65	F	75	¼	4½	Normal	Cholangeitis (mult. absc.)	++
19	61	F	70	7	10	1400	Cholangeitis (occ. absc.)	++
20	47	F	80	30	18	1800	Cholangeitis	++
21	34	M	55	4	15	2160	Toxic cirrhosis	+++
22	13	F	35	9	Biopsy	Normal	Toxic cirrhosis	+++
23	20	F	40	8	Biopsy	Normal	Toxic cirrhosis	+++
24	49	M	60	27	1½	1775	Toxic cirrhosis	+++
25	29	F	70	1	16	1180	Portal cirrhosis	+
26	57	F	90	1	Biopsy	Enlarged	Portal cirrhosis	+
27	32	M	65	3	Biopsy	Small	Portal cirrhosis	++
28	56	M	40	2	1	1400	Portal cirrhosis	++
29	42	F	90	11	Biopsy	Enlarged	Portal cirrhosis	+
30	37	M	50	2	2½	1560	Bil. cirrhosis	++
31	18	M	65	¾	9½	3000	Pigm. cirrhosis	++
32	37	M	25	1	11	1300	Subac. yellow atrophy	+++
33	62	M	20	1	2	800	Subac. yellow atrophy	+++
34	59	M	50	1	8	2200	Hepatoma	+++
35	53	M	70	29	4	2390	Hepatoma	+++
36	40	M	45	¾	1	1780	Bile duct carc.	+++
37	50	M	60	5	7	2700	Bile duct carc.	+++
38	52	F	25	1	19	Markedly enlarged	Metast. carc.	+++
39	66	M	65	26	11½	2370	Metast. carc.	++
40	57	F	60	14	8½	2910	Metast. carc.	+++
41	44	F	50	15	2½	1750	Miliary tbc.	++
42	28	F	25	¼	¾	2230	Leuk. infiltr.	+

* 0 = none. + = slight. ++ = moderate. +++ = marked.

It is of interest that the prothrombin concentration was slightly diminished in 4 of 5 patients in whom fatty infiltration of the liver was the only abnormality noted. The prothrombin concentration was within normal limits in 3 patients with cholangeitis, despite the fact that the inflammatory processes in the bile ducts were severe and had progressed in 1 instance to multiple abscess formation. However, in these latter cases the bulk of the parenchymal tissue appeared to be normal.

From these data there seems to be a better correlation between the prothrombin concentration and the histologic appearance of the liver than there is between the prothrombin concentration and the results of the hippuric acid liver function test.[6] The obvious deduction from these observations would appear to be that of these two

tests the prothrombin concentration is the less sensitive indicator of liver function, but the more accurate detector of actual parenchymal hepatic tissue destruction.

Summary. The prothrombin concentration was determined in 42 patients in whom the liver was examined at operation or at autopsy. Vitamin K was administered in adequate dosage to all those patients who had suffered from extrahepatic biliary obstruction. In general, the prothrombin concentration was normal when there was little or no destruction of the parenchymal tissue, and it was diminished when there was moderate or marked destruction of tissue. Exceptions to this rule are noted.

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PLASMA AMINO-ACID LEVELS IN HEALTH AND IN MEASLES, SCARLET FEVER AND PNEUMONIA.

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The question of the constancy of blood amino-acid concentration in diseases other than those of the liver has been reopened with the finding of plasma hypoamino-acidemia in young children with the

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nephrotic syndrome by Farr and MacFadyen[2] and in adults with pneumococcus pneumonia.[4] This has been due in part to the development of a highly specific and accurate method for the estimation of amino-acids by Van Slyke, Dillon, MacFadyen and Hamilton[9] and applied to blood and urine by MacFadyen, Van Slyke and Hamilton.[6] By this method the plasma amino-acid concentrations of patients with scarlet fever, measles and pneumococcus pneumonia have been compared with those from a group of apparently healthy individuals.

Materials and Methods. Nine patients with scarlet fever and 12 with measles were observed in the Willard Parker Hospital for contagious diseases. Eighteen patients with pneumococcus pneumonia were admitted to the pneumonia service of the Rockefeller Institute Hospital under the care of Drs. C. M. MacLeod, G. S. Mirick, and E. C. Curnen. No attempt was made to select these patients for study and in each instance the series represents consecutive admissions. Thirty apparently healthy individuals were observed at the Rockefeller Institute Hospital. This group was highly selected and carefully examined by physical examination and laboratory studies to exclude insofar as possible any disease. Both adults and children were included in the normal group, the ages ranging from $\frac{1}{2}$ to 45 years. The patients with scarlet fever or measles were predominantly children, while those with pneumonia were all adults from 25 to 62 years with the exception of an 11-year-old boy.

Blood was obtained from all patients at the time of admission. Blood was withdrawn from the scarlet fever patients following an overnight fast thrice during the first week and subsequently at weekly intervals. A second blood specimen was obtained from patients with measles after 1 week. The patients with pneumonia were bled on admission, the day following, and at selected intervals thereafter. The procedures followed in taking the blood were as previously reported.[4] On the 30 apparently healthy persons the blood was withdrawn after an overnight fast.

Plasma amino-acid nitrogen was determined by the ninhydrin CO_2 method of MacFadyen, Van Slyke and Hamilton.[6]

Results. The results are summarized graphically in Figure 1 and averages by each group with observed range and standard deviation are shown in Table 1.

TABLE 1.—AVERAGE PLASMA AMINO-ACID NITROGEN CONCENTRATIONS IN INDIVIDUALS WITHOUT APPARENT DISEASE, PATIENTS WITH PNEUMOCOCCUS PNEUMONIA, SCARLET FEVER, AND MEASLES.

	No. patients.	No. observations of plasma amino-acid nitrogen.	Average value plasma amino-acid nitrogen, mg./100 cc.	Standard deviation.	Observed range of plasma amino-acid nitrogen, mg./100 cc
Normal persons	30	31	4.47	± .46	3.75–5.56
Pneumonia (at time of discharge)	18	18	4.11	± .41	3.29–5.16
Pneumonia (at time of admission)	18	36	3.10	± .55	2.25–4.49
Scarlet fever	9	29	4.25	± .66	2.97–5.59
Measles	12	18	4.05	± .60	3.19–5.27

In none of the 30 apparently healthy individuals was the plasma amino-acid nitrogen concentration below 3.75 mg. per 100 cc., and

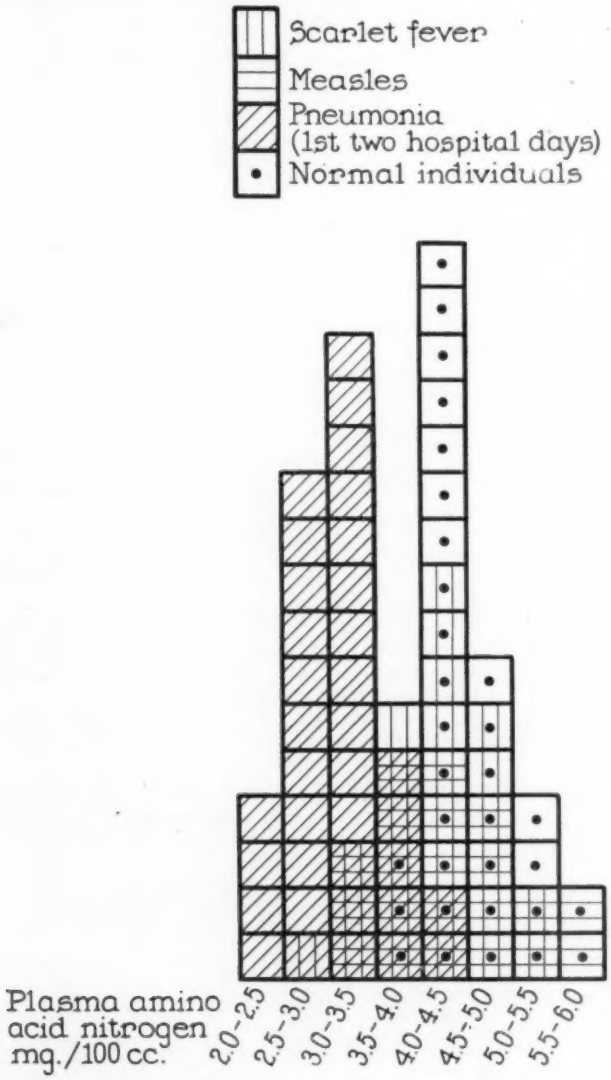

FIG. 1.—Distribution of fasting plasma amino-acid nitrogen values. Each square represents 1 patient, the varying markings indicating the type of patient.

in only 3 was the concentration below 4 mg. per 100 cc. The average plasma amino-acid nitrogen concentration in this group was 4.47 mg. per 100 cc.; the standard deviation was ±.46, and

the observed range 3.75 to 5.56 mg. plasma amino-acid nitrogen per 100 cc. There was no apparent change in the plasma amino-acid nitrogen concentration with increasing age. Until further data are obtained we have taken 4.50 mg. per 100 cc. as the average plasma amino-acid nitrogen concentration of normal healthy persons and have assumed concentrations to be within normal limits when differing from the normal average by an amount less than, or equal to, twice the standard deviation.

With but 4 exceptions, the 29 determinations made on the 9 patients with scarlet fever fell within the range of concentration of the healthy individuals. Each of the 4 exceptions occurred in a different patient. In 1 patient a concentration of 3.37 mg. per 100 cc. was found on admission. Subsequent determinations made on plasma from this patient over a 2-week interval were 4.35 mg., 3.58 mg. and 3.66 mg. per 100 cc. The latter two values fall just within the range defined as normal. In addition to scarlet fever, this patient had pseudohypertrophic muscular dystrophy. Another patient in the scarlet fever group had a low plasma amino-acid nitrogen concentration of 3.31 mg. per 100 cc. which occurred at the time he developed serum disease. Determinations of plasma amino-acid nitrogen in this patient made during the week prior to development of serum disease were 4.70 mg. and 4.35 mg. per 100 cc. Seven days subsequent to the serum sickness the plasma amino-acid nitrogen concentration was 4 mg. per 100 cc. In 2 other patients single determinations, both made on admission, were 3.39 mg. and 2.97 mg. per 100 cc. In the first patient the plasma amino-acid nitrogen concentration rose during the following week to 4.61 mg. per 100 cc. and 1 week later was 5.59 mg. per 100 cc. No further estimations were made on the second patient.

In the 12 patients with measles, all but 1 of the 18 determinations of plasma amino-acid nitrogen concentration fell within the normal range. In this instance, the low concentration of 3.19 mg. per 100 cc. occurred at a time when the patient developed a rise in temperature with coarse rhonchi and râles over both lung fields but with no roentgenologic evidence of pneumonia. A previous determination on this patient was 3.86 mg. per 100 cc.

Of the 36 determinations of plasma amino-acid nitrogen made on 18 patients with pneumococcus pneumonia on the first and second day in the hospital, all but 7 were below the normal range. Of these 7, 2 were from a patient with a very mild illness. Of the remainder, the first blood sample was obtained from 5 different patients admitted on the fourth, sixth, seventh, eighth and ninth day of disease, respectively. As previously pointed out, a near normal value would be expected in such patients at this time. When discharged only 1 of the 18 patients with pneumonia had a plasma amino-acid nitrogen concentration below 3.5 mg. per 100 cc. She

had pulmonary tuberculosis and over a 2-month period of observation, her plasma amino-acid nitrogen concentration remained quite constant at about 3.30 mg. per 100 cc.

Comment. Although the values of plasma amino-acid nitrogen in patients with measles and scarlet fever were occasionally below the levels usually found thus far in normal individuals, it is evident from a study of the data presented that no significant plasma hypoamino-acidemia is usually associated with either scarlet fever or measles. This is in sharp distinction to our observations on patients with pneumococcus pneumonia and patients with the nephrotic syndrome.[1-3]

The possibility exists that plasma hypoamino-acidemia was not observed in patients with scarlet fever or measles because the observations were not made sufficiently early in the disease course. The time of onset of pneumonia can be determined fairly accurately by the chill that occurs in most patients, whereas the diagnosis of scarlet fever or measles cannot be made with certainty during the preëruptive phase. An additional 24 hours usually elapses after the characteristic rash appears before the patient is brought to a hospital. Since in patients with pneumonia, the plasma amino-acids may return to near normal levels by the fifth day of disease, in this study we have not been able to exclude the possibility of a hypoamino-acidemia in scarlet fever and measles during the preëruptive phase.

The data in the present study cannot readily be compared to that of previous workers[5] because of differences in the analytical methods used. In a majority of published studies, colorimetric procedures have been used which Van Slyke and Kirk[8] have shown to be unreliable. The experiences of Farr and MacFadyen[2] with the Van Slyke nitrous acid method[7] have shown that its lack of specificity in comparison with the ninhydrin CO_2 method may, under certain circumstances, give misleading results. A rational explanation for plasma hypoamino-acidemia in some diseases cannot be formulated until more is known of the mechanism controlling amino-acid metabolism and concentration.

Summary. Thirty-one determinations of the plasma amino-acid concentration of 30 normal, apparently healthy individuals averaged 4.50 mg. per 100 cc. by the ninhydrin-CO_2 method. The standard deviation was $\pm .46$, and the observed range 3.75 to 5.56 mg. per 100 cc.

In patients with pneumococcus pneumonia, the plasma amino-acid nitrogen concentration was found to be low at the time of onset. With recovery from pneumonia the plasma amino-acid concentration returned to the normal range. Patients admitted to the hospital after the fourth day of disease failed to show significant plasma hypoamino-acidemia.

In patients with scarlet fever and measles, the plasma amino-acid nitrogen concentration was usually within the normal range. How-

ever, because of the difficulty of ascertaining the time of onset of these diseases, the data do not exclude the possibility of a plasma hypoamino-acidemia during the preëruptive phase of these diseases.

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EOSINOPHILIC GRANULOMA AND CERTAIN OTHER RETICULO-ENDOTHELIAL HYPERPLASIAS OF BONE.

A Comparison of Clinical, Radiologic, and Pathologic Features.

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Following the first reference in 1929, additional cases of a certain peculiar, solitary, destructive lesion isolated in the skull and other bones of children and young adults have been described as a supposedly new disease under the names of eosinophilic granuloma or solitary granuloma of bone. In 1930, Mignon[28] described a "granulations tumor" in the forehead of a 12-year-old boy, and in 1938, Schairer[32] reported 2 cases of "osteomyelitis with eosinophilic reaction." A publication by Otani and Ehrlich,[29] describing 7 cases, was quickly followed by Lichtenstein and Jaffe's[27] account of 4 cases. Hatcher[17] observed 3 cases, Kernwein[21] 1, and the Case Records of the Massachusetts General Hospital[4] contained 1. Very recently Farber[9a–c] listed 5 cases of solitary destructive lesions of granulomatous character in bone, and Bass,[1b] in the latest publication on this subject, reported 2 cases and quoted Dr. R. H. Jaffe as having observed 1 case. Altogether 22 cases have been recorded in the literature. Of these, 12 have been described in more or less detail, the other 10 cases were merely mentioned as having been observed.

Unnecessary alarm may result and needless extensive surgery may be done unless the possibility of so-called eosinophilic granuloma of bone is kept in mind when sharply delimited, destructive, solitary bone lesions are encountered in children or young adults. Although a malignant process is frequently suggested roentgenographically, all reported cases have terminated by complete healing and cure.

Case Report with Solitary Lesion.* CASE 1.—A white schoolboy of 15 had noted a soft lump on the right forehead for 2 months. It had grown slowly to the size of a walnut and was accompanied by local pain and tenderness. There was no history of trauma and he was in excellent health otherwise.

The patient was a normal, asthenic type of youth with a movable, soft, tender swelling about 4 by 4 by 1 cm. in size situated 5 cm. above the right orbit in the frontoparietal region. The skin was not attached to it.

Roentgenograms of the skull (Fig. 1) showed a solitary, sharply-outlined, irregular, rounded area of bone destruction in the right frontoparietal region of 2.5 cm. in diameter. The inner table showed greater involvement than the outer, suggesting pressure from inside the cranium. The adjacent bone and the rest of the skull appeared normal. Although a definite diagnosis was not made, secondary neoplasm was considered. Careful search revealed no evidence of a primary tumor. Blood count, urinalysis and blood chemical examinations, including cholesterol, were not abnormal.

Exploration revealed friable, yellow, soft tissue, forming a mass about 4 cm. in diameter underneath the periosteum. Following removal of part of this tissue, a hole 1.5 cm. in diameter was seen in the skull through which the underlying dura and brain appeared normal.

As received in the laboratory the material consisted of several pieces of soft, pinkish-gray tissue which formed a mass 1 cm. in diameter.

Histologically, the tissue was composed of heavily vascularized reticulo-endothelial tissue profusely infiltrated by leukocytes and large mononucleated phagocytes. A large majority of the leukocytes were eosinophils, which, although diffusely distributed, were more densely congregated about vessels (Fig. 2). The nuclei of the stromal cells were large, somewhat variable in outline, with delicate nuclear membranes and finely divided chromatin material. Mitotic figures are absent. The cytoplasm of the stromal cells, while abundant, stained light pink and was, in many instances, foamy in character.

The large mononucleated phagocytes possessed rounded and well-defined cell walls while the nuclei resembled those of the stromal cells. The cytoplasm contained vacuoles, large, irregular granules, erythrocytes or eosino-

* We are enabled to report this clinical case through the courtesy of Dr. J. R. Johnston.

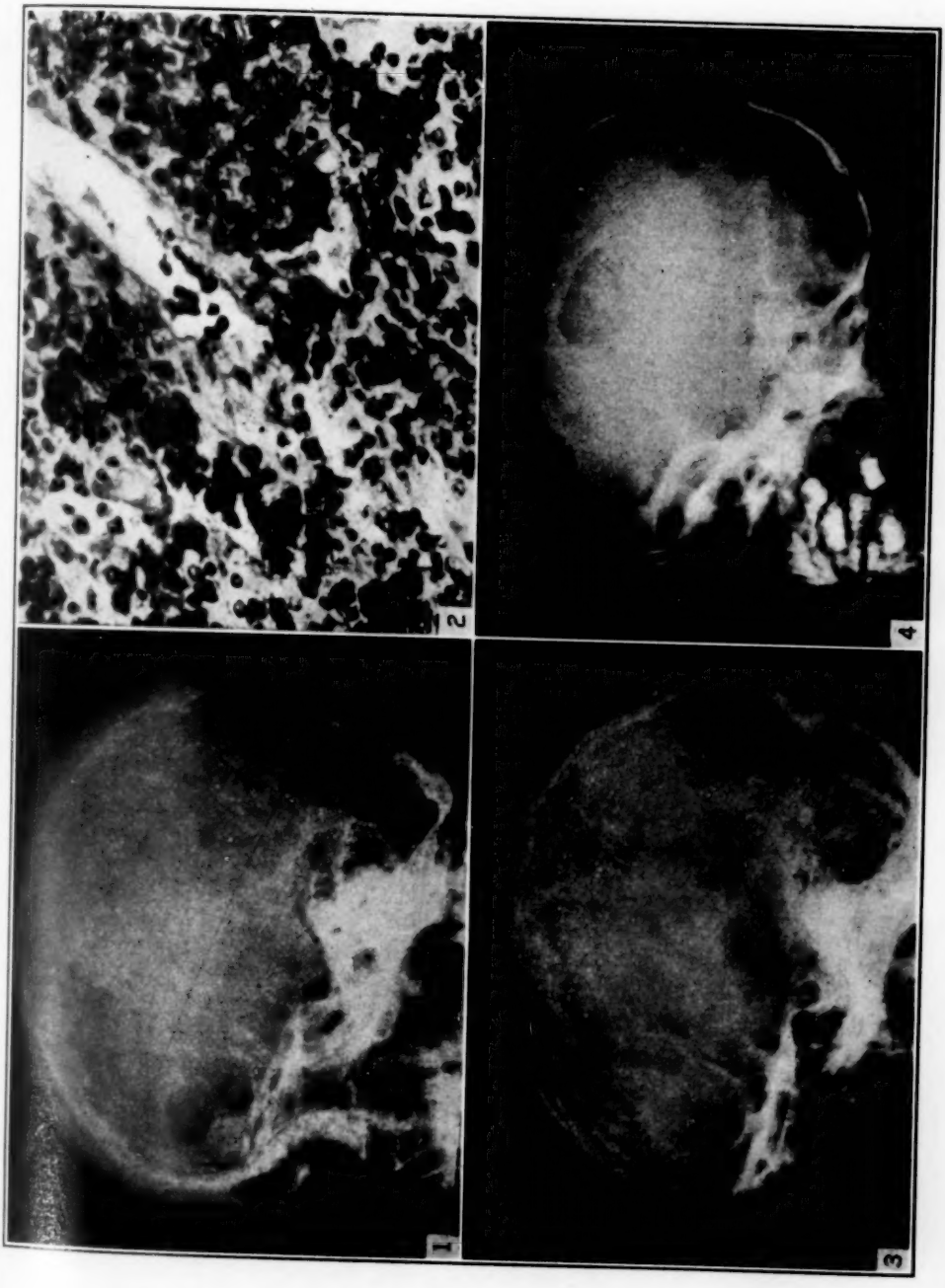
LEGENDS FOR ILLUSTRATIONS ON FACING PAGE.

FIG. 1.—Case 1. Lateral projection of skull showing a solitary, sharply-outlined, irregular, rounded area of bone destruction in the right fronto-parietal region.

FIG. 2.—Tissue from skull defect of Case 1, showing reticulo-endothelial tissue heavily infiltrated by eosinophilic polymorphonuclears (darkly staining cells). The infiltration is most pronounced about vessels. (Methylene blue-fuchsin stain.)

FIG. 3.—Case 1. Skull examination 16 months later, demonstrating complete healing and no new areas of involvement.

FIG. 4.—Case 2. Typical "geographic" skull as seen in Hand-Christian's disease.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philic granules. Occasional giant cells with peripherally arranged nuclei were found.

The vessels were thin-walled, frequently sinusoidal in type with large lumens. The endothelial cells lining the lumens were considerably swollen. Small hemorrhages were numerous.

Lymphocytes were infrequently seen. There were no areas of necrosis or fibrosis. No evidence of new bone formation was observed.

No bacteria could be demonstrated in the sections. Because the entire biopsy material was used for paraffin impregnation no fat stains were made.

Hand-Schüller-Christian's* disease and monocytic myeloma were considered as diagnostic probabilities and a number of prominent pathologists to whom the sections were submitted agreed with one or the other of these diagnoses.

About 2 weeks after operation a short course of high voltage Roentgen therapy was given. This consisted of a total of 1000 Roentgens (measured in air) applied in 5 daily exposures of 200 r each within a week to a field 6 by 8 cm. in size over the right frontal region.

Check-up examination 2 months after treatment showed alopecia over part of the treated area and a well-healed, depressed scar about 4 cm. in length. There were no other abnormalities.

At the last examination 16 months later, there was complete return to normal, both clinically and radiographically (Fig. 3).

Comment. Of the 16 recorded cases of so-called eosinophilic granuloma, in which the age was indicated, all but 3 were younger than 21 years. Of the latter, 1 was 21; 1, 24; and 1, 35 years old. Ten cases were male and 3 female. The sex of the other cases was not given. In 11 instances the lesion involved the skull; 5 of these, the frontal bone. The long bones were affected 5 times; ribs, 5 times; and the scapula, once. The bone lesions were commonly the only abnormality found and laboratory tests, with the exception of differential white blood cell counts, were normal.

Pain was mentioned as a prominent symptom in 7 cases. In 4 instances trauma to the site of the lesion was said to have antedated the appearance of the lesion. However, in several cases no history of trauma could be elicited, and in other reports no mention was made of trauma. The duration of the lesions, as indicated in the histories, varied from 10 days to 2 months.

The roentgenograms were commonly interpreted as suggestive of either osteomyelitis or tumor. In 6 cases subperiosteal bone formation was noted, while in 5 other cases notations were made of the absence of bone reaction.

A differential white blood cell count revealed a 4% to 11% eosinophilia in 7 cases. In one report[32] eosinophilic infiltration was found in a lymph node near the lesion; in another instance[27] the sternal bone marrow showed an increase in eosinophils. Examination of the feces of 1 case[10] disclosed a helminthic infestation which was regarded as the cause of the eosinophilia. Four reports noted a normal percentage of eosinophils in the peripheral blood.

* Hereafter the condition will be referred to as "Hand-Christian's" disease in keeping with preferable American usage.—EDITOR.

Grossly, the biopsy material from these lesions has been described as soft, cellular tissue, yellow-brown, gray-white, or gray-pink in color. With the exception of relatively minor details the histologic description in the various reports has been remarkably uniform.

The degree of phagocytic activity exhibited by the stromal cells, the presence or absence of multinucleated giant cells, mitotic figures, areas of necrosis, of scarring or of newly formed bone are details which vary somewhat in different reports. Such variance, however, may be explained on the basis that the biopsies represent different stages of the granulomatous process.

Before a lesion is classified as a separate and distinct pathologic entity, its distinguishing characteristics should be compared with those of related diseases in order to determine whether or not such segregation is justified.

The present study considers certain generalized hyperplasias of the reticulo-endothelial system as well as of the solitary xanthoma of bone which may be considered as a focal hyperplasia of reticulo-endothelial cells. Of the former, both the lipoid and non-lipoid varieties come under discussion.

Hand-Christian's Disease. This is usually a more or less generalized hyperplasia of the reticulo-endothelial system, of the lipoid variety. However, it is common knowledge that in this condition the classical triad—defects in the bones of the skull, diabetes insipidus and exophthalmos—may be incomplete. Indeed, some of the reported cases have none of these.

Other reported cases of Hand-Christian's disease raise the question of whether or not the reticulo-endothelial hyperplasia need necessarily be generalized. It seems possible, for instance, that in an early stage the disease may be represented by a solitary lesion. Such cases have been reported.[6,25,31,41] In 1 of these[25] Schüller himself agreed with the diagnosis. Furthermore, Farber[9b] encountered 4 instances of solitary bone lesions in which the patients later developed multiple lesions. The difficulty of differentiating this type of Hand-Christian's disease from the so-called eosinophilic granuloma, or the solitary xanthoma of bone is apparent. This difficulty was appreciated by Farber[9a-c] who, following critical study, was led to conclude that eosinophilic granuloma of bone and Hand-Christian's disease "represent variations in degree, stage of involvement and localization of the same basic disease process."

As relatively few cases of eosinophilic granuloma of bone have been studied it would appear premature to state definitely that this lesion will always be solitary. Likewise, it would seem unreasonable to classify the eosinophilic granuloma of bone as a new and distinct entity because the lesion is solitary, and at the same time ignore its similarities or even its identity in other respects to related conditions. Our view, which is in full agreement with that of Farber,[9a-c] is that the so-called eosinophilic granuloma of bone is probably

identical with what has been recognized as instances of Hand-Christian's disease in which the bone lesions are solitary.[6,95,25,31,41]

Case Report with Multiple Lesions. CASE 2.—A 4-year-old white girl was admitted to The Western Pennsylvania Hospital on January 25, 1934, suffering from a discharging left ear, prominence of the left eye and a stiff neck. The drainage from the left ear began a year and a half before admission, continued for 2 months and was followed by stiffness of the neck which lasted for 3 months. In the meantime the child apparently was well. One month before admission there was recurrence of the stiff neck, and a gradually increasing prominence of the left eye. Also at this time a soft spot on the left side of the child's skull and two small yellow spots in the left upper eyelid, not found previously, were first noticed.

The past and family histories were irrelevant.

The physical examination was negative except for the head, ears, eyes and neck. Several soft areas of various size were palpable in the frontal, parietal and occipital regions, suggestive of craniotabes. Both ears were dry, the canals being filled with soft wax plugs, but no pus was found when these were removed. Two small yellow intracutaneous plaques were found in the left eyelid. An ophthalmologist noted the left eyeball was slightly proptosed and displaced downward. There was 3 mm. of exophthalmos of the left eye as measured with the exophthalmometer (Hertel). The pupils, pupillary reactions and extraocular movements were normal. No palpable orbital masses were found, the fundi were not abnormal, and the media were clear. The child held the neck flexed and supported its head with its hands, but an orthopedic surgeon found motion of the cervical vertebræ free and without pain. A neurologist could demonstrate no neurologic syndrome.

Repeated blood counts showed a slight persistent eosinophilia (4%) but no other abnormalities. The Kahn test on the blood and spinal fluid of the patient as well as serologic tests of the mother and father were negative. The blood chemical examinations, including calcium, phosphorus and cholesterol were normal. Stool examinations and numerous urinalyses showed nothing abnormal. The highest temperature at any time was 37.4° C., but was usually normal.

Skeletal roentgenograms revealed multiple destructive lesions of the skull and left femur. Numerous defects in these bones with smooth edges produced the typical "geographic" skull seen in Hand-Christian's disease (Fig. 4). There were extensive areas of decalcification in the frontal, parietal and basal regions, especially on the left side. One of the large destroyed areas extended into the left side of the foramen magnum and probably accounted for the discomfort and deformity in the cervical region. The normal bone architecture was gone in the area about the left mastoid

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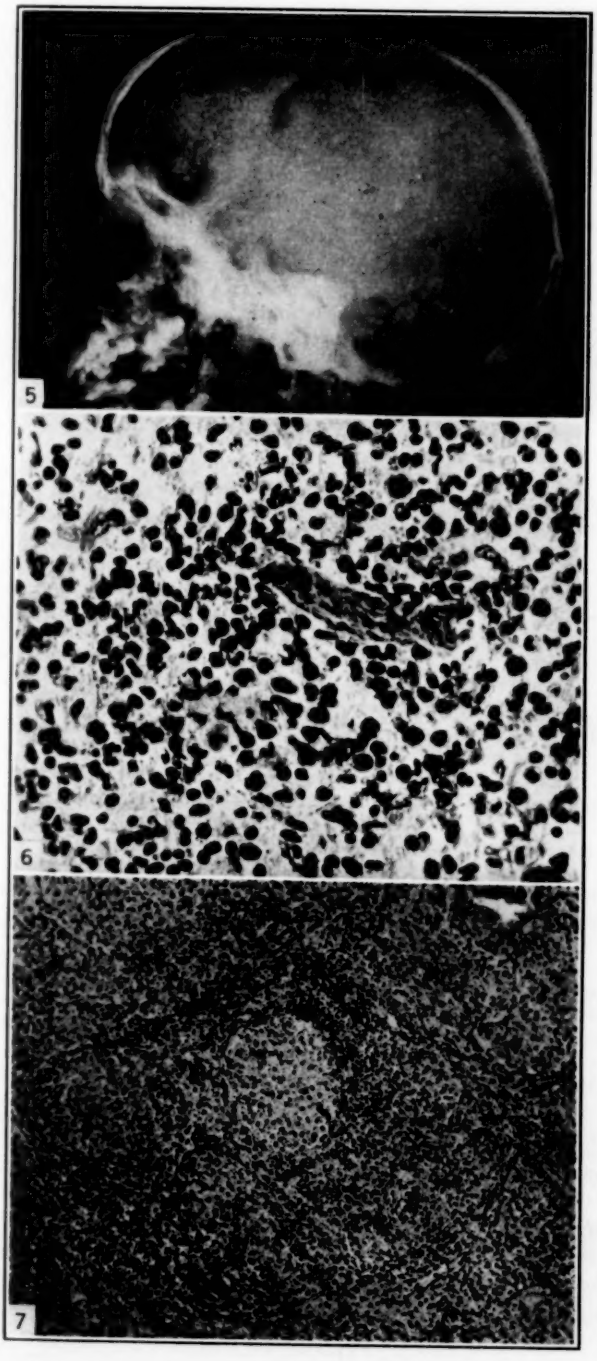
FIG. 5.—Case 2. Skull 2½ years later with return to normal and no new areas. Condition remains the same after 7½ years. No direct irradiation was given over the frontal or parietal regions.

FIG. 6.—Tissue from skull defect of Case 2, showing reticulo-endothelial tissue profusely infiltrated by eosinophilic polymorphonuclears (darkly staining cells). The intercellular granular material is composed of eosinophilic granules from disintegrated leukocytes. No foam cells are present. (Hematoxylin and eosin stain.)

FIG. 7.—Lymph node from Case 3, showing replacement of most of the lymphoid tissue by proliferated reticulo-endothelial cells, diffusely and nodularly distributed. There is an associated increase in fibrous tissue. No foam cells are present. (Hematoxylin and eosin stain.)



process and no air-containing cells were found. In the lesser trochanter of the left femur were several irregular cystic areas of bone destruction. A Roentgen diagnosis of Hand-Christian's disease was made.

A biopsy specimen, about 2.5 cm. in diameter, and including the thickness of both tables, was obtained under ether anesthesia from one of the decalcified areas in the right parietal region of the skull.

A short course of high voltage Roentgen therapy was given 2 weeks later. This consisted of a total of 250 Roentgens to each of six long, narrow portals, cross-firing the neck and spine in 6 days. The lesions in the frontal, parietal and femoral regions received no direct irradiation.

The patient made a steady recovery, gained in weight and successive roentgenograms showed complete return to normal (Fig. 5). No new lesion ever appeared, and no further treatment was necessary. At the present time, 7½ years later (July, 1941), the child is living and is normal except for diabetes insipidus, facial deformity and carious teeth. The diabetes insipidus has been present since an attack of whooping cough in 1936, but is now about half as bad as it was then. The urinary output varies from 3½ to 7 liters per day at present.

The biopsy specimen consisted of soft, red tissue which measured 3 by 2 by 2 mm., and small fragments of bone.

Microscopically, the material was composed largely of dense collagenous tissue, the cellularity of which varied considerably in different fields. The greater portion of the collagenous connective tissue was poorly cellularized, relatively avascular and hyaline in character. There were, however, small, circumscribed areas, like little islands, which were composed of closely packed mononucleated phagocytes, polymorphonuclears and occasional lymphocytes. The majority of the leukocytes were eosinophilic (Fig. 6). Numerous eosinophilic granules, apparently derived from disintegrated leukocytes, were found between the cells and also within mononucleated phagocytes. The latter possessed abundant pale cytoplasm but without the slightest suggestion of foamy appearance. In contrast to the paucity of vessels in the adjoining tissue, these islands of inflammatory cells contained numerous congested capillaries.

Furthermore, portions of the dense connective tissue showed non-circumscribed infiltrations by a large number of lymphocytes and pyknotic, spindle-shaped cells. Adjacent to several of these infiltrations, trabeculæ of bone were seen which showed loss of nuclei and pronounced decalcification. The edges of these trabeculæ were marked by small, irregular defects which contained granular, acidophilic material. This gave the trabeculæ a "moth-eaten" appearance.

In contrast to the above picture, a large trabecula of bone with a smooth and oval outline and otherwise normal appearance was seen only a few low-power diameters away from the regions of bone destruction. The periphery of this trabecula was delimited by a zone of closely applied, scattered osteoblasts and by dense periosteum-like tissue. The surrounding collagenous connective tissue was relatively acellular and avascular. In short, the picture in this region was that of quiescence and complete healing.

No evidence of new bone formation was seen. The destroyed bone was apparently replaced by dense collagenous tissue. No giant cells were found in the sections. No examination was made for the presence or absence of lipoids or fat.

Comment. The similarity microscopically between the lesion of the second case and that of the first is striking. Probably the greatest difference is in the presence of scar tissue in the second, and the absence of dense collagenous tissue in the first case. The difference

is readily explained by a difference in the stage of the disease process as indicated by Farber.[9a-c] The small cellular islands found in the second case represent active foci of the disease and they are absolutely identical with the type of tissue found in the first case.

Our belief in the probable identity of the two diseases is based mainly upon the fact that the histologic features regarded as characteristic of eosinophilic granuloma of bone are also found in Hand-Christian's disease. Both conditions show destruction and replacement of normal tissues by granulomatous tissue in which endothelial cells predominate. The latter may contain lipoid. In an analysis of 84 cases of Hand-Christian's disease reported in the literature, we have found 9 in which lipoid-containing cells or "foam cells" were not found in the biopsy or autopsy material and in 26 cases neither the presence nor the absence of these cells was mentioned.

The participation of eosinophilic leukocytes is common to the lesions of both conditions. It was noted in 29 of the 84 cases of Hand-Christian's disease analyzed by us and in 5 of 7 such cases studied by Farber.[9b] Not infrequently this eosinophilic infiltration was regarded as pronounced.

Eosinophilia of the peripheral blood has been noted with eosinophilic granuloma.[4,10,27,28,32] In the 84 cases of Hand-Christian's disease analyzed by us eosinophilia was noted in 13 cases; 3% in 3,[7,36,37] 4% in 5,[2,20,24,30,40] 5% in 1,[5] 6% in 3[9b,19,25] and 7% in 1 case.[14]

Hand-Christian's disease is, at times, associated with a hypercholesteremia. Out of a total of 45 in which the blood cholesterol content was indicated, 23 cases had a level of over 200 mg. per 100 cc. Insufficient data are available regarding this point in eosinophilic granuloma of bone.

Visceral involvement in Hand-Christian's disease is common. It is interesting to note that we have found 2 cases[23,30] in the literature in which there was soft tissue involvement but no radiologic evidence of bone lesions. Since no autopsies have been performed on cases of eosinophilic granuloma of bone, little can be said about visceral involvement in this condition. However, reports of eosinophilia in a draining lymph node,[32] in sternal bone marrow,[27] as well as in the peripheral blood[4,10,27,28,32] indicate that in addition to the solitary osseous lesion in eosinophilic granuloma of bone there may be more widespread and even systemic changes.

In both types of lesions various stages of healing with the production of osteoid tissue and bone may be encountered. There may be very little of pathognomonic significance and no essential difference in the histologic appearance of the lesion of either condition. As a matter of fact, some radiologists have discouraged biopsy in Hand-Christian's disease because the histologic picture of the lesion in this disease has been nondescript and inconclusive on occasions.

The radiologic appearance of the osseous defects in Hand-Christian's disease is very similar to that of eosinophilic granuloma. The

only difference appears to be that in the former the lesions are usually multiple and in the latter disease there is a solitary lesion.

As in Hand-Christian's disease the lesion of eosinophilic granuloma may progress spontaneously or with irradiation. Unlike the 30% case mortality of Hand-Christian's disease, all reported cases of eosinophilic granuloma have recovered.

Letterer-Siwe's Disease. This is a non-lipoid reticulo-endotheliosis considered by some writers identical with infectious reticulo-endotheliosis. It has certain similarities to Hand-Christian's disease and to eosinophilic granuloma. Letterer-Siwe's disease affects infants and children predominantly and is nearly always fatal. From a radiologic point of view the osseous lesions of this disease are identical with those of Hand-Christian's disease. Histologically, the lesions are usually devoid of lipoid, but cases[8,39] have been reported where small amounts of lipoid were present within the reticulo-endothelial cells. On the other hand, biopsies from lesions of Hand-Christian's disease may also show little or no lipoid.

Case Report of Non-lipoid Reticulo-endotheliosis.* CASE 3.—A 13-month-old, white, female infant was admitted to the St. Vincent Charity Hospital of Cleveland because of splenic and generalized lymph node enlargement.

The past history was not significant except that for 6 months previously the infant had been eating poorly and for a number of days prior to admission there had been dyspnea at night.

The patient's weight on admission was 7550 gm. (16.6 pounds). There was a discharge of partially crusted material in both external auditory meati. The drums were hyperemic. Examination of the chest disclosed no abnormality. The spleen was enlarged and extended 4 cm. below the costal margin. The cervical, axillary and inguinal nodes were enlarged and discrete.

The red blood cell count varied from 4.2 to 2.5 million during hospitalization. The concomitant hemoglobin determinations varied from 72% to 34%, and the platelet counts from 270,000 to 366,000. There was no eosinophilia.

During hospitalization the infant had successive showers of cutaneous petechiæ. The spleen enlarged progressively and reached to the iliac crest shortly before death. The lymph nodes also became larger.

Roentgenologic examination of the chest disclosed enlargement of the thymus and a diffuse mottling in the lung fields, suggestive of miliary tuberculosis.

The temperature varied between 37.5 and 38.5° C. with occasional peaks of 39.5°, and a terminal rise to 41°. Death occurred 5 months after admission.

A *biopsy* of a cervical lymph node performed 3 months before death showed a remarkable degree of endothelial hyperplasia which was diffuse and nodular. Many giant cells were present. This appearance was mistakenly interpreted as that of hyperplastic tuberculosis.

The significant *autopsy* findings consisted of the following:

Innumerable cutaneous petechiæ were present.

The thymus was much enlarged and its normal, lobulated architecture

* Presented by one of us (P. G.) before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, May 4, 1934.

replaced by trabeculated hemorrhagic tissue which contained irregular yellow foci.

The lungs were honeycombed by smooth-walled cysts 3 to 7 mm. in diameter and the lower lobes were consolidated.

The liver was enlarged and showed fatty change.

The spleen was greatly enlarged, rounded, blue-red in color, firm in consistency. The cut surface showed a variegated red and yellow, firm, somewhat trabeculated tissue which replaced the normal splenic architecture. The yellow areas were in the form of miliary and larger conglomerate nodules.

Lymph nodes, everywhere, were enlarged and on section showed small, opaque yellow foci.

The lymphoid apparatus throughout the intestinal tract was tremendously hypertrophied.

Postmortem roentgenograms of the skull showed defects in both parietal bones. The largest was about 2 cm. in diameter.

Microscopically, sections of spleen, liver, lymph nodes, thymus, lung and intestinal tract showed replacement, or infiltration, or both, by cells of the endothelial type. In addition to a diffuse type of infiltration, nodules resembling those seen in Boeck's sarcoid were present in lymph nodes, spleen and thymus (Fig. 7). In these organs the endothelial hyperplasia was also associated with a pronounced increase in fibrous tissue particularly in the capsule and pericapsular region. In the liver and lung the proliferation of endothelial cells was less striking, but, nevertheless, pronounced. There was associated, extensive fatty metamorphosis throughout the liver while the lung exhibited irregular thickening of alveolar walls and peribronchiolar tissue by proliferated endothelial cells which resulted in numerous large, cyst-like, emphysematous cavities. A considerable portion of both lungs, particularly throughout the lower lobes, showed more diffuse infiltration by endothelial cells, which filled the alveolar spaces and gave the tissue the appearance of pneumonic consolidation.

The proliferated endothelial cells were frequently large, oval, rounded, or polygonal, and possessed deeply acidophilic cytoplasm. Some cells contained hemosiderin. No foam cells were found. A pronounced tendency to form many multinucleated giant cells was present in the spleen and thymus. This was less marked in the lymph nodes and lung, and absent in the intestinal tract and liver. The spleen and thymus also exhibited many mitotic figures and considerable pleomorphism of the endothelial cells as well as many areas of necrosis and hemorrhage. These changes suggested a transcendency of hyperplasia to neoplasia. However, the absence of such changes in the proliferated endothelial cells elsewhere and their relative uniformity in other organs gave the impression that the original and indeed the picture as a whole was that of simple hyperplasia.

Silver impregnation stains showed a pronounced increase in the reticulum, the fibers of which frequently tended to surround the individual endothelial cells.

The Sudan IV stain revealed that occasional cells were filled with fine droplets of fat, some cells contained only a few droplets while the vast majority of the proliferated cells contained no stainable fat.

Comment. The clinical syndrome exhibited by Case 3 of lymph adenopathy, splenohepatomegaly, cutaneous petechiæ, bone defects, hypochromic anemia, fever and rapid down-hill course includes practically all the important features of Letterer-Siwe's disease (nonlipoid reticulo-endotheliosis).

The microscopic picture, with the exception of neoplastic changes

in the spleen and thymus, is clearly consistent with this concept. It is not unusual in this disease to find small amounts of fat in the proliferated endothelial cells. The pulmonary changes of Case 3 have been more commonly seen in Hand-Christian's disease. The sarcomatous changes in the thymus and spleen are considered incidental and terminal.

The difference between the lipoid and the non-lipoid varieties of reticulo-endotheliosis may, on first impression, seem adequate. However, a study of the reported cases reveals, as Wallgren[39] has stated, that these differences are not greater than the variations in pathologic anatomy between different cases of the same disease. He further emphasized that neither of the two diseases has any characteristic feature that cannot occur in the other. What seems to us a logical view is expressed by both Wallgren[39] and Glanzmann,[13] who look upon Hand-Christian's disease as the chronic form, and upon Letterer-Siwe's disease as the acute form of reticulo-endotheliosis. The paucity of lipoid in Letterer-Siwe's disease is explained on the basis of its rapid course.

The connecting link between Letterer-Siwe's and Hand-Christian's disease is formed by those cases[11,15,18,35] possessing features intermediate between the two diseases. Several of these[15,35] exhibited eosinophilic infiltration as a component of the osseous lesions. The connecting link between Letterer-Siwe's disease and eosinophilic granuloma of bone is represented by the case reported by Guizetti.[16] A 3-month-old infant had a solitary lesion of the humerus which showed the histologic picture of eosinophilic granuloma of bone. In addition, the body of this infant showed visceral lesions characteristic of infectious reticulo-endotheliosis.

Solitary Xanthoma of Bone. We have found in the literature 7 cases of solitary xanthomatous lesions of bone. In 5,[3,22,33,34,38] the histologic diagnosis or description indicated the presence of lipoid granulomatous tissue in the lesion. One[1a] was said to be a pure xanthoma without admixture of granulomatous aspects and another[22] was said to be a "typical xanthoma" which, in addition, contained an abundant amount of hemosiderin. In 3 cases[3,22,142] the blood cholesterol was elevated: 224 mg., 274 mg., and 300 mg., per 100 cc., respectively.

The presence or absence of eosinophilic leukocytes in the lesion was not mentioned by any of the reporters. Inasmuch as the infiltration by eosinophilic leukocytes was either not mentioned or treated very casually in most of the reports dealing with Hand-Christian's disease, little significance can be attached to this omission in cases of solitary xanthoma of bone.

From a histopathologic point of view there may be nothing else to differentiate this type of lesion from that of eosinophilic granuloma or of Hand-Christian's disease. Roentgenologically, no significant difference may exist between the appearance produced by the lesions of

solitary xanthoma, eosinophilic granuloma and the individual lesions of Hand-Christian's disease and Letterer-Siwe's disease.

Prognosis. Given a patient with a solitary bone defect of the type seen in the reticulo-endothelioses a biopsy is necessary to establish the probability as a fact. If the microscopic picture is that of lipoid reticulo-endotheliosis, the lesion heals, and if no subsequent ones appear within a year the chances that the patient is cured are good. If, however, other lesions develop there is approximately a 30% probability of a fatal outcome.

If the microscopic picture is that of non-lipoid reticulo-endotheliosis, Hand-Christian's disease cannot be ruled out because lesions elsewhere in the body may be quite characteristic of the latter.[12,15] However, if the osseous lesions are associated with an acute and rapidly progressive clinical course characteristic of so-called non-lipoid reticulo-endotheliosis the probability of a fatal issue is nearly 100%.

General Considerations. Of the various lesions under discussion those of Hand-Christian's disease are the most common. Nevertheless, even the latter is so infrequently encountered that the average pathologist has little familiarity with it. It is not surprising to find that this disease has been diagnosed tuberculosis, osteitis-fibrosa, luetic osteitis, carcinoma, sarcoma and multiple myeloma.

On the other hand, the literature also contains statements which imply considerable confidence in ability to arrive at the correct diagnosis. The statements "no other condition causing destructive lesions in the skull in children has simulated it" (Hand-Christian's disease), and "the diagnosis was uncertain until *x*-ray showed the presence of Hand-Christian's disease" indicate that either the writers were not familiar with other reticulo-endothelioses or they considered the latter identical with the former.

The presence of small amounts of lipoid in the endothelial cells does not exclude non-lipoid reticulo-endotheliosis. How much lipoid a lesion of this disease may contain and still deserve its classification has not been defined. It has been customary to classify the lesion as lipoid reticulo-endotheliosis if "foam" cells or cholesterin-needle spaces are present.

It appears that our knowledge of the diseases involving reticulo-endothelial proliferations, whether focal as in eosinophilic granuloma or solitary xanthoma, or more generalized as in Hand-Christian's disease or Letterer-Siwe's disease, is far from complete. Biopsies should therefore be encouraged rather than discouraged.

The similarity in histopathologic features of eosinophilic granuloma on the one hand and solitary xanthoma as well as Hand-Christian's disease on the other, is quite close and warrants placing these conditions in the same general disease group.

There does not seem to be any observed distinctive roentgenographic or pathologic feature nor other decisive information at

present regarding any one of these lesions to justify their dogmatic segregation into separate disease entities.

Likewise, the existence of cases with features intermediate between Hand-Christian's disease and Letterer-Siwe's disease (or infectious reticulo-endotheliosis) raises the question of whether or not a sharp distinction between the lipoid and the non-lipoid reticulo-endothelioses is valid.

Conclusions. 1. Eosinophilic granuloma of bone is not a new nor distinct entity. It is a reticulo-endotheliosis and is probably identical with those cases of Hand-Christian's disease which have been reported to have had solitary lesions. It is also closely related to certain other reticulo-endothelial hyperplasias.

2. The interrelationship demonstrated between eosinophilic granuloma and solitary xanthoma of bone, Hand-Christian's and Letterer-Siwe's disease and the existence of cases with features interimedate between these so-called entities make sharp distinctions between them of doubtful validity.

3. Since there are no pathologic, roentgenographic or other decisive features known at present which are distinctive for any one of these reticulo-endothelioses, the need for further study, including routine biopsy, in this type of case is apparent.

4. Three case reports are presented which illustrate the variations in degree, stage of involvement and localization of reticulo-endotheliosis.

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THE TOXICITY OF FLUORINE IN DICALCIUM PHOSPHATE.*

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Dicalcium phosphate is used as a dietary supplement during pregnancy, and for infants and children. Since fluorine is present in dicalcium phosphate as an impurity due to the sources of raw material or methods of manufacture, obstetricians and pediatricians should give consideration to the possibility of chronic fluorine poisoning.

It appears unlikely that a contamination as great as 0.5% or 5000 parts per million, would be encountered in dicalcium phosphate prepared by a responsible manufacturer. However, even such a high degree of contamination would not be likely to cause acute fluorine poisoning, since a dose of 2 to 4 gm. of dicalcium phosphate would represent an intake of only 10 to 20 mg. of fluorine. An acute reaction would be all the more improbable because of the large excess of calcium. Therefore, the problem requiring attention is one of chronic poisoning which differs from acute fluorine poisoning both as to symptoms and mechanism of action.

An interesting feature of fluorine toxicosis is the difference in symptomatology and mechanism of action between acute poisoning and chronic poisoning produced by continued ingestion of fluorides over a period of time. For the purpose of this report interest in acute fluorine poisoning centers in the fact that an acutely toxic dose of fluoride lowers the level of blood calcium and produces the symptoms characteristic of a decrease in blood calcium. The administration of calcium chloride or lactate is a satisfactory anti-

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dotal measure. In sharp contrast is the fact that chronic fluorine poisoning resulting from continued ingestion of fluorides is not characterized by a drop in the blood calcium level. Moreover, there is no conclusive evidence that calcium administration alleviates the symptoms of chronic fluorine poisoning.

The most striking and most easily observed symptom of chronic fluorine poisoning is bleaching of tooth enamel, known as enamel dystrophy or mottled enamel. This dental defect has been repeatedly demonstrated in rats and dogs, and occurs in man under conditions where fluorine has been ingested more or less continuously in the drinking water during the time that the permanent teeth were being laid down. While this dental defect is the most readily observed injurious effect produced by the continued ingestion of fluorine, it is by no means the only undesirable effect. The review by Kaj Roholm[9] presents adequate evidence of the deleterious effect of fluorine on the bony structures in general.

Evidence obtained both *in vivo* and *in vitro*[1] in this laboratory strongly suggests that the fundamental mechanism involved in chronic fluorine poisoning is an inhibitory action on bone phosphatase activity. The recent report by Wilson, DeEds and Cox[15] on cadmium toxicity lends support to the idea that an inhibition of phosphatase activity is intimately associated with the impairment of calcification. It was shown by Wilson and DeEds that the continued ingestion of cadmium by albino rats produced a bleaching of the incisors indistinguishable from that caused by fluorine. The possibility that the bleaching of rat incisors might be caused by a sensitization of the rats to the action of small amounts of fluorine normally present in the diet, rather than to the cadmium *per se*, was not conclusively ruled out. However, the demonstration *in vitro* that cadmium in a concentration of 10^{-3} N equivalent to 112 parts per million, reduced the activity of a bone phosphatase preparation to 8% of the activity in the absence of cadmium, strongly suggests that cadmium *per se* can produce the same lesions in bony structures as does fluorine.

If the cation cadmium *per se* can produce the same defect in tooth enamel that is produced by the anion fluorine, it seems unlikely that the defect is due to a deficiency of calcium. A more fundamental mechanism must be postulated to account for an abnormal calcification produced by either a cation or an anion. The important deduction to be made is that an abundant or excessive intake of calcium might not be expected to counteract the toxic action of continuously ingested fluorine.

Present Studies. An excellent test of the effect of an increased calcium intake on the chronic toxicity of fluorine is the determination of the toxicity of fluorine as found in dicalcium phosphate.

A patent has been granted to M. H. Merchant[4] for the removal of fluorine compounds from bone liquors. It is pointed out in this

patent that the fluorine content of dicalcium phosphate as ordinarily prepared from bone liquors may run as high as 1000 parts per million, or even more, and that good dicalcium phosphate of commercial grade preferably contains not more than 0.03%, or 300 parts per million. Merchant states that, since fluorine is considered objectionable in foods, or in chemicals to be used for human consumption, it is desirable to reduce the fluorine content of dicalcium phosphate to as low a value as possible, such as 20 to 40 parts per million.

The sample of dicalcium phosphate used in this study was supplied by the Food and Drug Administration. Their analyses showed a fluorine content of 0.27%, or 2700 parts per million. The possibility of a toxic action traceable to the fluorine in the dicalcium phosphate was tested by incorporating the material in various concentrations in a well balanced diet[16] and feeding it to groups of albino rats.

Twenty albino rats (12 females and 8 males) were divided into four groups containing 3 females and 2 males each. All the rats were of approximately the same age, being born within a period of 5 days. The rats were quite uniform in weight (average, 41.7 gm.). Each group of rats was placed in a cage permitting free access to water and food at all times. Four diets were prepared containing 3, 6, 12, and 24 gm. of dicalcium phosphate per kilo of diet, corresponding to 8.1, 16.2, 32.4, and 64.8 parts of fluorine per million parts of diet respectively. One group of rats was placed on each of these diets, and observations were made on an average of once a week for changes in the coloration of the incisor teeth.

When the incisor teeth of the young albino rat first erupt they are completely white. Even at the age of 30 days, when the rats weigh 40 to 50 gm., the incisor teeth have little of the color characteristic of the adult rat. During the next 20 to 30 days the anterior enamel surface of the incisors darkens rapidly until it reaches the depth of color seen in the normal adult rat. The final increase in coloration is a slow process.

The fluorine present in all dosage levels of dicalcium phosphate used adversely affected the normal rate of coloration of the rat incisors. A concentration of 0.3% dicalcium phosphate, corresponding to 8.1 parts of fluorine per million parts of diet, slightly retarded the rate of tooth coloration for the first 30 days and subsequently actually produced a definite degree of bleaching as compared with the controls. Doubling the concentration of dicalcium phosphate gave a fluorine concentration of 16.2 parts per million and caused a bleaching of the rat incisors as early as the 15th day. The bleaching developed rapidly after the 30th day. Levels of dicalcium phosphate corresponding to 32.4 and 64.8 parts of fluorine per million parts of diet produced a final degree of bleaching only slightly more severe than that resulting from 16.2 parts of fluorine per million, but the bleaching action became evident much

earlier, especially on the highest fluorine intake where little coloration of the incisors appeared at any time.

The dosage levels of dicalcium phosphate used were determined by the known fluorine content, and the previously reported fact[2] that 14 parts of added fluorine, in the form of sodium fluoride, per million parts of diet produced unmistakable bleaching of rat incisors in all rats. The obvious conclusion from the results in this report is that the fluorine content in dicalcium phosphate is as readily available for production of chronic toxicity as is the fluorine in sodium fluoride. The calcium and phosphate had no demonstrable antidotal effect. The results support the claim that chronic fluorine poisoning is not associated with calcium depletion.

Possible Clinical Significance. For purposes of supplementing the diet with calcium and phosphorus, the recommended daily dose of dicalcium phosphate for a period of weeks or months is $\frac{1}{4}$ to 1 teaspoonful for infants, and $\frac{1}{2}$ to $1\frac{1}{2}$ teaspoonsful for children. Let us assume that the average daily dose of dicalcium phosphate is 1 teaspoonful, or approximately 60 grains, equivalent to 3.8 gm. The dicalcium phosphate sample used in this investigation had a fluorine content of 0.27%. This means that the average daily dose of approximately 4 gm. of dicalcium phosphate would represent a daily fluorine intake of 10 mg. Moreover, it must be borne in mind that this fluorine intake is superimposed upon that which is unavoidably ingested with food and water, and which represents a variable and unknown amount. It has been reported that drinking water containing 1 part of fluorine per million can produce mottled enamel in children. If the average daily consumption of such water is assumed to be 1 liter, approximately 1 quart, it is seen that a daily fluorine intake of 1 mg. produces mottled enamel in at least some children. Therefore, an average daily dose of 1 teaspoonful of dicalcium phosphate having a fluorine content of 0.27% represents a fluorine intake 10 times the amount known to be injurious to the teeth. This conclusion is supported by the results of this investigation which have shown that the fluorine in dicalcium phosphate is as physiologically active as is fluorine in sodium fluoride.

A brief review of the pertinent reports in the literature on fluorosis will supply the background of information which, from the viewpoint of the obstetrician and pediatrician, gives added significance to the results herein reported. These reports are concerned with the maternal transfer of fluorine, the effects in the newborn and on the deciduous teeth, evidence on the mechanism of fluorosis, and evidence for effects other than the production of mottled teeth.

In an earlier report from this laboratory[1] it was shown that the bones of young rats suckled by mothers receiving sodium fluoride in the diet exhibited a decrease in phosphatase activity as compared with controls. In harmony with this observation is the report by Robison and Rosenheim[8] that a concentration of 0.00001 M

sodium fluoride in the perfusion liquid inhibits calcification *in vitro*. Murray[5] has reported that the average fluorine content of the bodies of five litters of rats born of mothers receiving 0.05% sodium fluoride in their diet was significantly higher than the average fluorine content of five litters born of normal mothers. Murray concluded that the amount of fluorine transferred *in utero* was large enough to be harmful in the light of the calcification studies by Robison and Rosenheim.[8] Murray[5] has also demonstrated the transference of fluorine during lactation. The possibility of fluorine poisoning during uterine life has also been investigated by Velu[13] who concluded that young animals born from mothers exposed to the influence of fluorine develop dental alterations which must have originated during the time before birth. Smith and Smith[11] have reported on the occurrence of mottled enamel on the temporary teeth of children living in a district where the water supply contained from 12 to 18 parts of fluorine per million. However, these authors state: "Severe mottling of the enamel of the temporary teeth has since been found in the breast-fed infants. This points to the passage of fluorine into the fetal system or into the milk supply of the nursing mother. Again, the fluorine concentration of the water supply was found to be excessively high."

It is outside the scope of this report to review all the evidence related to the changes in teeth and bone produced in chronic fluoride poisoning. For a more detailed account and references the reader is referred to the excellent review of Kaj Roholm.[9] However, the conclusions of several investigators may be given. For instance, Sutro[12] studied the changes produced in rats and concluded that the changes produced in teeth and bones are due to a chemical disturbance unrelated to the parathyroid glands. This author believes that the appearance of osteosclerosis in both clinical and experimental chronic fluoride poisoning may throw some light on the etiology of idiopathic osteosclerotic diseases. Schour and Smith[10] have concluded that fluorine probably exerts a direct local action on the enamel-forming cells, and that the observed changes in the enamel and dentine are not produced primarily by changes in blood calcium and phosphorus or by disturbances in the parathyroids. Phillips, Hart, and Bohstedt[7] studied fluorosis in dairy cows, and showed that a fluorine intake in excess of 3 mg. per kilo of body weight greatly reduced milk production, that reproduction was unaffected, but that there was a delay in the appearance of estrus after parturition and a lower body weight in the newborn calves.

For the most part, interest in the effects of long-continued ingestion of small amounts of fluoride has centered in the changes produced in bones and teeth, especially the latter because the changes are more obvious, although they may not be the more serious. It has been shown by Wilson and DeEds[14] that thyroid exerts a syner-

gistic action on fluorine toxicity, and DeEds, Wilson and Cutting[3] have shown the same to be true of thyrotropic hormone. Not only is there a hormonal relationship to fluorine poisoning, but there may be other and far-reaching effects due to the fact that fluorine is a general protoplasmic and enzymatic poison. Phillips and Hart[6] studied the effect of organic dietary constituents upon chronic fluorine poisoning in the rat and concluded that the mode of action of fluorine is systemic in character and is produced by a general inhibition of enzymic systems, and that fluorine may interfere with, or disturb, the actively metabolizing systems involving phosphoric acid esters.

The sample of dicalcium phosphate used in this investigation was obtained in 1937 and had a fluorine content of 2700 parts per million. Hence, an average daily dose of 60 grains (or 3.8 gm.) represents a fluorine intake 10 times the amount known to be injurious to teeth. Therefore, the fluorine content of dicalcium phosphate should not exceed a maximum of 0.02%, or 200 parts per million. No information is available regarding the fluorine content of dicalcium phosphate on the market at the present time (1941).

Summary. 1. The toxicity of fluorine present in dicalcium phosphate has been investigated, using the bleaching of rat incisor teeth as a criterion of injurious action.

2. The fluorine present in dicalcium phosphate has been shown to be as physiologically active as fluorine administered as sodium fluoride.

3. An average daily dose of 1 teaspoonful of dicalcium phosphate containing 0.27% fluorine represents a fluorine intake 10 times as great as the amount said to produce mottled enamel in at least some children.

The author is indebted to the Food and Drug Administration, Federal Security Agency, for data on the fluorine content of 16 samples of dicalcium phosphate prepared before July, 1939, by various American manufacturers. The fluorine content of these samples, expressed as parts per million ranged from 11 to 498, and 9 of the 16 samples ranged in value from 30 to 66.

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THE RESPIRATION IN MYASTHENIA GRAVIS.

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In the past few years our knowledge of the pathophysiology of myasthenia gravis and its treatment by prostigmine has been greatly increased by many publications, especially those of M. B. Walker,[9] Boothby,[2] Kennedy and Moersch,[4] Viets and Schwab,[8] and Minot, Dodd and Riven.[6]

Comparatively few observations have been made of the function of breathing in patients with myasthenia gravis, although the respiratory muscles are often involved in these subjects, giving rise to disturbing and occasionally alarming symptoms. K. Mendel[5] commented on the roentgenologic evidences of respiratory changes in persons with myasthenia gravis. Albertoni[1] noted the presence of Cheyne-Stokes respiration in this condition, while Minski and Stokes[7] used kymographic respiratory curves to demonstrate the beneficial effect of prostigmine. Gammon and Scheie[3] studied the effect of prostigmine upon the height to which a mercury column could be blown. In contrast to other central or peripheral lesions studied so far, the authors found only in patients with myasthenia gravis a definite improvement. They advocate therefore the use of prostigmine as a diagnostic test for this condition.

We studied some aspects of the respiratory function in 5 subjects with classical myasthenia gravis. Two of these patients suffered from recurrent severe suffocative attacks characterized by extreme restlessness, a feeling of anxiety, pale cyanotic discoloration of the skin, rapid feeble pulse, fever, and labored breathing. The rapid shallow breathing during an attack was carried on predominantly by the accessory respiratory muscles with very little movement of the chest or diaphragm and was interrupted by a continuous dry hacking cough. Wheezing râles were present over the entire chest and numerous rhonchi were audible in the bases. This syndrome may be considered as an atelectatic pneumonia induced by the inefficient breathing apparatus.

We were interested in ascertaining the degree of disturbance in breathing in myasthenia gravis and in determining whether simple tests of the respiratory function could be used for gauging the severity of the disease. The following functions were studied in 5 patients with myasthenia gravis: 1, The vital capacity, its changes in relapses and during remissions induced by prostigmine. 2, The muscular and diaphragmatic movements as determined by

roentgenographic methods. 3, The degree of oxygenation of the arterial blood.

The vital capacity fluctuated widely in the same patient but was distinctly low in all 5 cases. In general, the more severe the myas-

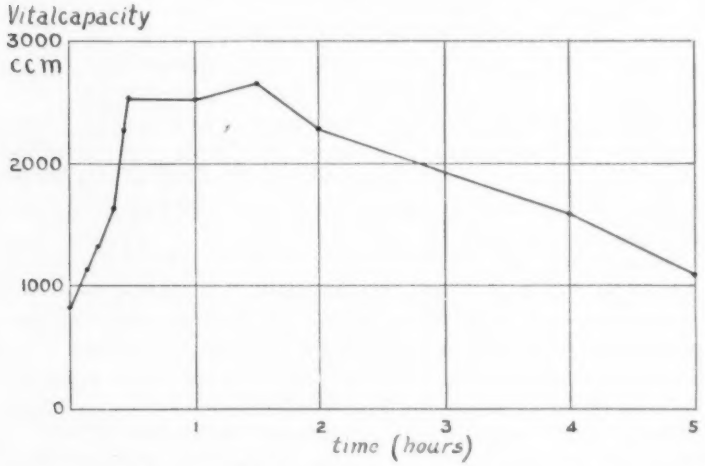

CHART 1.—Increase of vital capacity in myasthenia gravis after subcutaneous administration of 0.001 gm. prostigmine.

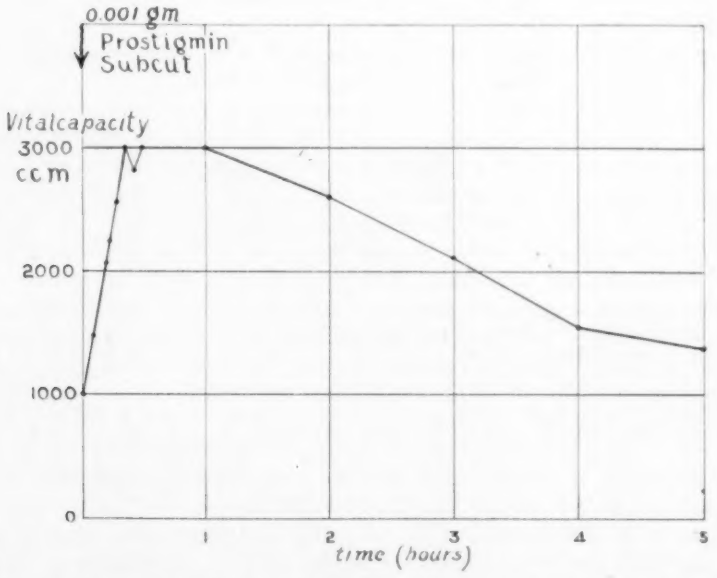

CHART 2.—Increase of vital capacity in myasthenia gravis after subcutaneous administration of 0.001 gm. prostigmine.

thenia the lower was the vital capacity. In the 2 severest cases exceptionally low values (400 to 500 cc.) were observed, while during the suffocative attacks the vital capacity could not be measured. Injection of prostigmine in these subjects was followed by a prompt rise in vital capacity, occurring simultaneously with the improvement in the patient's general condition. This reaction is illustrated graphically in Charts 1 and 2.

TABLE 1.—CORRELATION BETWEEN VITAL CAPACITY AND MUSCULAR FUNCTION FOLLOWING PROSTIGMINE.

Time (min.).	Vital capacity.	General condition.
Before prostigmine	1100	Dysarthric speech, lid lag, difficulty in swallowing, passive recumbent position, arms can be raised to 20-degree angle
	Injection of 0.5 Mg. Prostigmine Subcutaneously.	
2	1400	Arms can be raised to 45-degree angle
6	1600	Can look up, speech unhindered, swallowing possible
8	1900	Arms can be raised to 90-degree angle, patient can get out of sitting position and walk several steps unsteadily
10	1900	No change
20	2000	Can hold arms outstretched for several minutes, walking improved
23	2300	Can stretch arms, and walking, speech, ocular movements and swallowing normal
30	2400	No change
60	2500	No change
90	1900	Fatigue after 20 steps; maximum arm raising to 45-degree angle, mild ptosis
120	1700	Ptosis unchanged; arm raising to 30-degree angle; has to stop after walking 5 steps
180	1500	Arm raising to 30-degree angle, walking and standing impossible
240	1400	Unchanged
300	1200	Speech, swallowing and eye movements as before injection; patient cannot rise from recumbent position

The improvement in the vital capacity as well as in the general condition may be noted within 10 minutes after the injection of prostigmine and may last several hours.

For some unknown reason the response to prostigmine varies in different individuals and in the same individual from time to time. It is important to note, however, that changes in the vital capacity paralleled closely the changes in other muscular functions. This correlation is illustrated in Table 1. It is typical of reactions which we have observed repeatedly in these patients following the administration of prostigmine.

This parallelism was observed in the spontaneous remissions which frequently occur in this disease, as well as in those induced by prostigmine, clinical improvement being reflected in the increase in the values for the vital capacity. On the other hand, in several instances in which no marked clinical improvement followed the injection of prostigmine no appreciable change in vital capacity was detected.

The spirometric method may be used to demonstrate the efficacy of various therapeutic measures in myasthenia gravis. We found, for instance, that caffeine, strychnine, ephedrine, veratrine and inhalation of mixtures of CO_2 and O_2 had no distinct influence on the symptoms and signs in myasthenic patients who responded promptly to prostigmine.

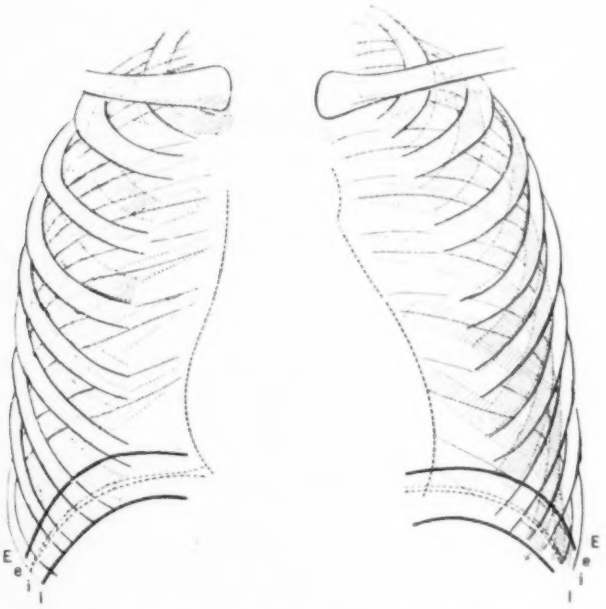

FIG. 1.—Myasthenia gravis. The diaphragma level on normal (.....i) and forced (———I) inspiration and normal (.....e) and forced (———E) expiration before prostigmine.

Roentgen ray and fluoroscopic observations were made by Dr. F. Fleischner on patients with myasthenia gravis in various stages and during periods of remission induced by prostigmine. When the vital capacity was diminished, the most striking abnormalities noted were: 1, Reduced motility of the diaphragm, amounting in severe cases almost to paralysis. 2, Elevation of the ribs and thoracic lordosis. 3, In severest cases signs of atelectasis. The prompt restoration to normal diaphragmatic and thoracic motion following the administration of prostigmine may be strikingly observed fluoroscopically. This reaction is illustrated in Figures 1 and 2.

The marked reduction in the breathing surface led us to investigate the question of arterial oxygen saturation. Blood was drawn in paraffined vessels from the brachial or femoral artery and analyzed for its oxygen content and oxygen capacity, using the method of Van Slyke. The results in 3 experiments are shown in Table 2.

It may be seen that despite the extreme reductions in vital capacity there is little or no diminution in the oxygen content or saturation. The hyperpnea, no doubt, compensates in part for the inefficient muscular action. The absence of hypoxemia despite the low vital capacity may be contrasted to the conditions which we observe in pulmonary edema or pneumonosis where arterial hypoxemia may

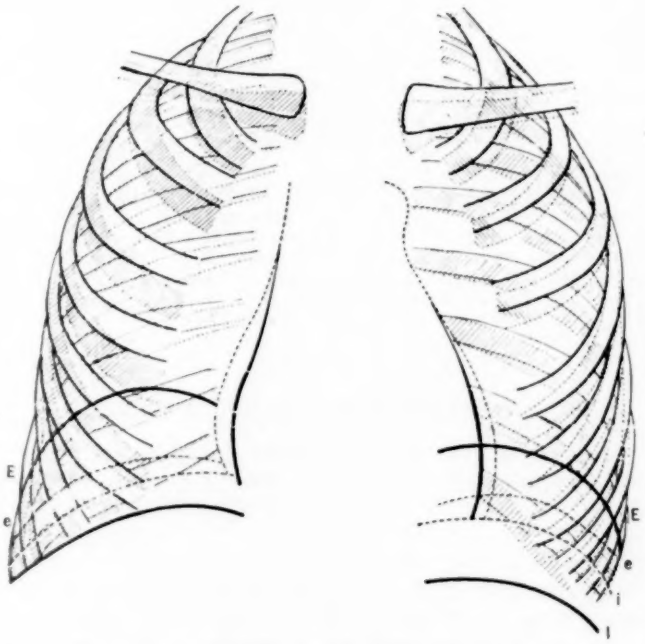

FIG. 2.—After subcutaneous prostigmine administration.

TABLE 2.—ARTERIAL O_2 CONTENT AND SATURATION, VITAL CAPACITY BEFORE AND AFTER PROSTIGMINE.

Patient.	O_2 content (vol. %).		O_2 saturation in % of total capacity.		Vital capacity (cc.).	
	Before Prostigmine.	After Prostigmine.	Before Prostigmine.	After Prostigmine.	Before Prostigmine.	After Prostigmine.
St. K. . .	15.74	16.79	95	99	600	2200
Fr. St. . .	16.95	17.72	92	99	1000	2600
M. D. . .	22.64	22.64	99	99	1000	2000

be present associated with vital capacities considerably higher than those recorded above. The arterial anoxemia in the latter is presumably due to difficulties in gas diffusion through the pulmonary alveoli. The absence of this barrier in our patients may serve to explain the apparently normal aëration of the blood in the lungs.

Measurement of the vital capacity is simple, objective and directed to a vital bodily function. It is recommended as a supple-

ment to the functional tests used in patients with myasthenia gravis to determine the severity of the disease and the efficacy of therapeutic agents.

Summary. Certain aspects of respiratory functions were studied in patients with myasthenia gravis. The vital capacity is greatly reduced due to inefficiency of the diaphragm and auxiliary muscles concerned in breathing. Changes in vital capacity parallel closely alterations in the general state. It may be used as a reliable measure of the severity of the disease and the efficacy of therapeutic procedures. Despite extreme reduction in vital capacity there is no apparent interference with oxygenation of blood in the lungs.

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THE INTESTINE AND CHRONIC ARTHRITIS.*

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Aurelianus, in the fourth century A.D., considered an arthritis as of gastro-intestinal origin with a hereditary predisposition. Paul of Aegnia regarded the intestinal tract with its disorders as contributing to both gout and arthritis. Popoff, in 1887, experimentally produced arthritis with streptococci, which has been confirmed by others. Burbank and Hadjopoulos, with an antigen from streptococci obtained from the blood and upper respiratory sources studied various infective foci remote from the intestinal tract. It has not been emphasized, however, that intestinal organisms might by their presence in the blood stream be a cause of joint disturbance and by way of continued reinfection assail the local and general immunity production forces.

There is no totally distinctive change in the generally recognized two types of chronic arthritis, which are usually recognized as having a wide overlap. The thickening and round cell proliferation of the synovial membrane, granulation over the synovia, adhesions with increase of fibrous tissue, involvement of the periarticular

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tissues, ankylosis and the cementing together of joints are seen in both types. The pathologic pictures in spondylitis is similar to that of joints and bones elsewhere in the body. Although the cases have similar changes, the predominance of one or other type warrants the use of the terms atrophic or hypertrophic. There is much about them that suggests some type of an infection as an important etiologic factor.

Not much credence has been placed in the value of skin reactions or allergic tests to bacteria to suggest the infective unit, and the same may be said about the presence of agglutinins and precipitins, to streptococci particularly. Paul[4] points to the concept of focal infection not playing a part in the continuation of the disease although the so-called "eradication of foci of infection" may be of benefit in the early stages of rheumatoid arthritis. Others believe that a focal infection may be a "precipitating" factor but that it is not the fundamental cause of the continuation of the disorder. This is suggested in that the removal of focal infections does not benefit the average chronic case, and if so, mostly in the indirect way of improving the general state of health. There is believed to be insufficient evidence that any of the organisms which may be demonstrated in a focal infection actually causes arthritis. Burbank states that he has demonstrated streptococci in the canaliculi of the cancellous tissue of joints; but in the vast majority of the cases this condition is not present and almost never late in the disease. There have been suggestions that it is a systemic disease in origin. For instance, arthritis may ensue in hyperthyroidism, the menopause, after coronary thrombosis, exposure to damp and cold, nervous shock, psoriasis, ulcerative colitis. This, however, does not eliminate the intestine as a cause.

We may agree that there is some clinical evidence that points to an initial infection starting arthritis, and, accepting the intestinal canal as one of the sources of this infection, that slow additions of bacteria, even if they do not successively lodge in the joints, may continue it. We have three substantiations for this assumption: 1, it is proven that bacteria pass through the walls of the intestine; 2, that even in clean cases the peritoneal cavity may contain intestinal bacteria; and 3, that intestinal bacteria may be found in the general blood stream. We would deal, then, with organisms in the digestive canal which gain the circulation and unless they are controlled in the intestinal tract, the results from most treatments would be limited. The process then would be an infection of the blood stream from the bowel and the lodgment of the bacteria in the canaliculi of the cancellous tissue adjacent to joint surfaces (where they are the smallest in the body) and the periarticular tissues, their destruction by local immunities causing a reactive change, and the local processes continuing in allergic ways by further blood stream infection or absorbed specific toxins from the bowel.

The high incidence of intestinal bacteria in the blood of one vein tap in non-arthritic as well as arthritic persons (5% to 8%),[1c,2] the remissive character of the disease and the benefits from intestinal treatments suggest this factor. The fact that the body often has to contend with intestinal bacteria in the blood stream and that only about 2% or 3% of the population in the United States becomes a victim of chronic arthritis, suggests that some people are more lucky than others in their immunity makeup, that there may be an hereditary or biologic resistance to an infection, or that many of the organisms are not joint selective in nature. Such assumptions are more reasonable to entertain than that there is some form of a "virus" as its fundamental cause, that rheumatic arthritis "is a systemic disease" of some mysterious nature, or that it is totally "metabolic" in cause. For the latter we have no bases of reasoning such as we have in the initial joint infection with the development of an allergy to the bacteria present in chronic arthritis.

In 1920[1b] attention was drawn to the colon in connection with chronic arthritis. Thirty-four cases of typical polyarthritis were described, in which but one improved noticeably from the removal of a focal infection above the clavicle, and 10 showed no evidence of focal infections. The clinical findings and methods of handling were described, and the results in the joints by the handling of a chronic biotoxic intestinal condition presented. Of these 44 cases, marked improvement was observed in 21, moderate in 19, and none in 4. Attention was drawn to arthritis and the colon in connection with type diets and infections with *C. welchii*, Gram-positive single and double cocci, *B. putrificum*, and pathogenic types of *B. coli*, staphylococci and streptococci. With apologies for quoting myself, the following was presented, "There is good reason to believe that in the early course of this disorder if attention is given to the colon, as well as to other focal infections, many would be saved a fate of chronic joint deformity and invalidism." But in the last 20 years the significance of streptococci as an etiologic factor in chronic arthritis has received pointed attention, and the writer now desires to modify his original conception of a chronic biotoxic intestinal state causing the disorder in a catabolic way, and agree to the bacteria themselves as probably the more important factor.

The writer[1d] drew attention to several types and strains of streptococci recoverable from the intestinal canal, those of the fecalis, mitis, equinus and hemolyticus types being most frequently found. Because of the variation ability of all streptococci when studied by cultural methods, sharp genus differentiation of the various types leaves doubts about the hemolytic, non-hemolytic and green-producing types being definite separate forms. The distinct blood-laking types (pyogenes, hemolyticus, hemolyticus I and II) are conspicuous in this mutation ability, and this no doubt is true with all streptococci. Of the various types (of which there are some 35

or more), all streptococci are hemolytic to some degree. The question here of hemolytic power is largely one of degrees, this commonly changing in what appears to be the same strain. There is evidence, however, that streptococci are common denizens of the intestinal canal in apparently healthy persons and that distinct high hemolytic forms are met with in about 7% of normal persons, and that when there is disease and disorder of function in the bowel they are met with more often. In 50 cases of ulcerative colitis, for instance, high hemolytic streptococci were met with in 42 cases, and the non-hemolytic and viridans in all. A factor of importance in the presence of pathogenic streptococci is that they are more often met with when certain other bacteria are present. These particularly are the organisms of the Eberthella, Salmonella, Shigella and Escherichia groups to which others to be mentioned can be included. In clinical medicine these symbioses appear to be an important factor in infections. Not only do certain organisms multiply freely in the presence of others, but also there is suggestion that added virulences and toxicities are acquired by the combination, such as is present in pulmonary tuberculosis for instance. In no part of all infections is this so important as it is with organisms in the intestinal canal. The more definite the incidence of a mixed infection, very probably the more definite is the etiologic significance of the streptococci. To appreciate the significance of streptococci in the bowel, it is necessary to study the association of these other organisms, because apparently streptococci in significant numbers do not continue in the intestinal canal without an associated infection to assist them. It is possible that non-streptococcic organisms recoverable from the blood stream would also have significance as enhancing and allergic factors in chronic arthritis. Most often the organisms recovered from the blood stream are streptococcic in origin, although morphologically and culturally they may not appear to be unless they are studied by different medias and after passing through several subcultures. A student of intestinal bacteriology can look with doubt upon any specific streptococcus causing rheumatoid arthritis, such as the Hastings-Bedell strain and that recently suggested by Cecil, Nicholls and Stainsby.[3] Burbank appears to be nearer correct when describing the ignavus, fecalis, viridans, infrequens, mitis, salivarius, equinus and subacidus, all of which are common denizens of the human intestinal canal and all of which are mutable. It is reasonable to believe that a streptococcus met with in the joints of chronic arthritis could have been one of the well-known more innocent strains initially and by mutation acquire a virulent factor and even different culturable abilities and staining characteristics. Often in blood cultures one seems to be dealing with a bacillus which on cultural observation ends up as a coccus. Even in the Gram-negative organisms mutation-like changes appear to be common.

A group of cases of chronic arthritis were studied and treated along biologic ways. These patients were placed upon a test diet (p. 94),[1c] casual stool specimens being considered unsuitable. This diet was maintained for 72 hours and a purged specimen used for culture studies. The stool first was examined for general character, reaction, food detritus, ova, and so on, and note made of the conspicuous types of microörganisms present. Specimens were then inoculated into different medias, more particularly as follows: For the streptococci, beef-heart infusion and with agar, beef blood and brain-dextrose broth; for the Eberthella, Salmonella and Shigella organisms, the MacConkey, bismuth-sulphate agar, tetrathionate broth, Ligler iron-agar or Krumwiede triple sugar agar were employed; for the coloniform organisms, egg meat mediums, endo, MacConkey's and Krumwiede media. A separate set of observa-

TABLE 1.—ANALYSIS OF 331 CASES OF ARTHRITIS (GENERAL GROUP).

Description.	No.	Acute.	Chronic.	Improved. Greatly.	Mod.	Not.
Cases eliminated for various reasons	37					
Cases in which a positive focal infection existed (other than intestinal) and initially treated as such*	109	11	98	24	19	66
Cases in which gonorrheal infections were possible; these are included in the focal infection Group 2†	6	..	6			
Cases in which the arthritis was considered as due to gout and treated as such‡	21	8	13	14	1	6
Endrocrine instances treated first by estrogens and other glandular products‡	92	7	85	16	18	58
Trauma and exposure considered important; treated by rest, splints, etc.§	9	..	9	2	..	7
Positive Wassermann and Kahn cases; treated for syphilis for 4 months§	5	..	..	2	1	2
Considered as gastro-intestinal initially	58					

* Of the acute cases they all improved satisfactorily. All of the moderate and non-improvement cases were treated intestinally subsequently.

† These were cases in which there had been a history or a possibility of this infection (eroded cervix), tender or swollen Fallopian tubes, pus cells in prostate strippings. Two were added to the intestinal group subsequently.

‡ The moderate and no improvement cases were added to the intestinal group subsequently.

§ The non-improved cases were added to the intestinal group subsequently.

tions for 10 days were made with lytic tubes containing 2% dextrose bouillon to study the incidence of phage action and to note the most persistent types or forms, those lysing in the first few days being regarded as not important. This method is also useful for subculture identifications. Other than the streptococci and staphylococci, the rest of the Gram-positive organisms (the strict anaërobic types) did not get much attention, as they were regarded as insignificant in a pathogenic sense in these cases. Three blood cultures apiece were made routinely in 100 cases, with several media. These were positive in 17% of the instances. As this was 8% on one vein tap and 12% on 2 taps, and 17% on 3 taps, a group of 25 cases of chronic arthritis was tapped weekly for 10 times and in these there were 11 positive, practically 44%. It seems reasonable to assume that if more vein taps were made a still higher percentage of positives would be noted, even accepting that our cultural methods are not

as satisfactory as could be desired. Ten vein taps were made on each of 25 healthy individuals for a comparison, here 12% being positive. Apparently in chronic arthritis the incidence of positive blood cultures is higher than in healthy cases. It would be interesting to know what the incidence of positive blood cultures would be in chronic disease other than chronic arthritis. Even then, however, the question of joint selectivity of bacteria and allergy could not be judged.

TABLE 2.—TOTAL OF 202 CASES TREATED GASTRO-INTESTINALLY (94 MALES, 108 FEMALES).

Description.	No.	Improved.		
		Greatly.	Mod.	Not.
Secondary biotoxic states due to various gastro-intestinal conditions other than primary biotoxic intestinal states and treated as such initially*	51	36	8	7
Considered as probably straight streptococci infections and treated as such with fecal streptococci as vaccines†	21	12	7	2
Primary biotoxic intestinal states of mixed infections treated as such	181	124	33	24

* The moderate and non-improvement cases are included in the primary biotoxic group.
† The 2 not improved were added to the biotoxic group.

According to the bacterial findings and significances, biologic treatment was set up, in as simple form as possible to be practical. Briefly they were as follows:

1. *Rectal Instillations.* On the bases that antagonisms existed between the strains of the *B. communior*, *B. aërogenes* and *B. acidilactici* of *Bacilli coli* (Dunham's classification) and the other strains of *Escherichia coli* and forms of pyogenic and zymogenic organisms[1a] (in which the Salmonella and Eberthella are included), bi-weekly rectal injections were employed in the cases all the way through the treatment. Fifteen cubic centimeters of a 24-hour growth in 2% dextrose bouillon of each (making totally about 15 trillion viable organisms) were made up to 100 cc. by the addition of a 1% dextrose solution, after which the patient rested on the left side for 15 minutes. In about half of the cases an insignificant drop in the leukocyte count of a fifth to a third was noticed at about 8 hours after the first few culture instillations. After about 2 months of treatment a subjective sense of fatigue may be complained of by the patient, and toward the end of treatment a few will present a slight amount of disorientation. This may be controlled by a moderate dose of aspirin after which the instillations should be stopped. The rule was that when the injected strains of *B. coli* continued growing in the colon, advantage was taken of the patient's selectivity to these organisms and cultures were made directly from the patient's stools and used instead of stock strains. This apparently is a distinct advantage.

2. *Oral Phages.* In all of the well-advanced and established cases, and when distinct benefit has not been brought about in a few weeks' time, a phage type of mouth administration was also employed. According to the observation made in lytic observa-

tions,* the time was noted when further phage treatment did not take place from day to day. The then persisting and resisting types of organisms were inoculated into 500 cc. of 2% dextrose bouillon, grown for 48 hours and sterilized by filtration through candle filters. Usually several filtrations were necessary for sterilization. Various chemicals were used to render this material safe from further bacterial growth, but none were so successful as care in the initial candle sterilization and very cold ice-boxing as a preservative. This product should only be used when crystal clear, and when it becomes the slightest bit foggy, it must be discarded. This phage product was taken each morning by mouth in 5 to 10 cc. quantities before breakfast, preceded and followed by a tablespoonful of olive oil. When distinct clinical benefit had been brought about, this item of treatment was modified and discontinued. It is impossible to state how this produces additional benefit, but that it is an item of considerable importance there is no question.

3. *Vaccines.* If the blood cultures showed the presence of Gram-positive cocci and at times if the stool specimens of lytic tubes suggested their prominence and persistence, concentrated vaccines were made and used intradermally and subcutaneously. These were not sterilized by heat. The washings from the surface of agar tubes (using for the purpose a small amount of the following mentioned merthiolate solution) were made up to about 5 times the volume with a 1 to 5000 merthiolate solution made up by the addition of sodium chloride to a physiologic salt solution. Such a mixture is bacterially sterile in 48 hours.

No effort was made to count the bacteria, local reactions being used to suggest the dose. The vaccine was started with 1 minim given with a tuberculin syringe and a very fine needle. According to the local reaction, the dosages were slowly increased usually at about 1 minim at a time and given twice a week. The dosages were kept short of pronounced reactions, small doses over longer lengths of time being regarded as a better plan. These were usually given midway between the rectal instillations although often were administered on the same day. In tight skins when the quantity given was greater than could be injected between the layers of the skin, the remainder of the dose was injected subcutaneously. There is also no way to estimate this biologic item of treatment; at times it seemed worthwhile but in many of the cases not so. The rectal and mouth types of treatments were depended upon more. In the

* Two ordinary test tubes were employed, each containing 15 cc. of 2% dextrose bouillon and inoculated with a streak on the side wall of the tube using a straight inoculating wire which had been plunged in feces. Tube 1 is the aërobic tube using the media as such. The contents of Tube 2 is boiled actively for a few minutes to drive out the largest percentage of air (oxygen) which the media has acquired on standing. The contents are rapidly cooled, inoculated as in Tube 1 and then covered with toluol or mineral oil. The latter is a fair type of anaërobic procedure, simple and found to be practical enough for this work.

cases of staphylococci and organisms other than the streptococci, the vaccines seemingly were more efficacious but accurate observations on this point are not possible to elucidate with sufficient degrees of accuracy. It is well known that streptococcic vaccines are notably ineffective for immunity production and it was deemed that the streptococci were not the total infection factor in chronic arthritis.

The suggestion from these cases was definite that when the symbiotic organisms were controlled, the streptococci in both the intestine and the blood stream was also controlled.

A purged specimen of stool was checked each month and the biologic treatments were modified or maintained according to the suggestion of the findings at these examinations and the clinical improvement. This stool checking was done for 4 or 5 months, after which the stool specimens are examined for 6 months after the discontinuance of biologic treatments. If the case was of the marked improvement type and then became worse again (chronic arthritis is a remissive disorder), a purged stool specimen (on the diet as initially) was again examined and the biologic set-up of treatment established according to the findings. There were usually several shifts or modifications in the biologic handling in the majority of cases.

The diets fundamentally followed the rule indicated in chronic biotoxic intestinal conditions. In the putrefactive or alkaline form, high carbohydrates and hydrocarbons and sharply limited proteins of readily digested forms were given; in the fermentation or acid form, high protein diets with limited carbohydrates (5%) and a severe control of hydrocarbons. Effort was made to control the total intake of food in those above normal weight (Medico-Actuarial Mortality Investigation, 1912), and additional foods urged in supplemental meals in those definitely below these standards. This was not followed too strictly, because in the obese debility may ensue, and in the underweight the digestion often became embarrassed. Calcium in any form was regarded as contraindicated; foods as low in calcium content as possible were selected. No attempt was made to benefit an anemia with iron-bearing foods but by liver and iron therapy. The bowels were moved by lactose, dextrins, food roughages, and agar, but mineral oil preparations and the salines were not employed. Cascara, low simple enemas and occasional small doses of calomel were employed. Colonic irrigations were not used, and where definite clinical food allergies existed these foods were avoided.

Treatment was influenced by the pathogenic bacterial findings, and more particularly directed toward influencing symbiotic types rather than only definite strains. Of these microörganisms, in addition to the Eberthella, Salmonella, Shigella and Escherichia, *Strep. alcaligenes*, Gram-positive enterococci (both single and double) and *Etherobacilli Prodigiosus* were of interest. It was assumed that

the last named, though less than Eberthella, Salmonella, Shigella and Escherichia, might act as symbiosing and enhancing factors with streptococci, but no special attention was paid to them. On the whole, this symbiosing factor on the part of the bacteria with streptococci is impossible to estimate accurately. All one can do is to assume in the individual case that such a possibility exists and that their presence may act as enhancing, conversion or mutation factors to the streptococcic infection (the *Strep. fecalis*, for instance) thereby rendering these more innocent forms of streptococci important as infecting agents. It is reasonable to assume that the average person should develop immunities against low-grade infections better by natural means than could be accomplished by therapeutic immunity procedures. Yet clinical medicine suggests this is not always accomplished, and that biologic measures can produce active immunities. While a "gang member" in arthritis is in all probability some form of streptococci, they would not be important without the supporting and enhancing bacteria that are associated with them. In this sense the streptococci are only part of an associated infection and perhaps even only that of a secondary invader.

Another point of importance is that various conditions in the digestive canal can bring these bacterio-toxic factors about in a secondary way. Pemberton and others have drawn attention to ptosis, angulation, gall-bladder disease, constipation, and so on, being significant in connection with the subject of chronic arthritis. Here, however, we deal with gastro-intestinal or medical conditions in which the content of streptococci and even the symbiotic infections are possible of being corrected by attention to the disorder resident in the digestive tract. Especially is this observed where normal transit through the colon, or incomplete bowel evacuations exist. While ameliorating in the majority of instances, the correction of these did not always produce marked enough amelioration of the chronic arthritis, although at times it was striking. It thus is obvious that the treatment of these more strictly gastro-enterologic states would be in order initially in every instance of chronic arthritis. The cases treated biologically were all primary in type.

Twenty cases were treated by the various sulphanilamide preparations, 6 with moderate improvements lasting a short time. Apparently a few cases of arthritis will improve on this therapy possibly by controlling the streptococcic systemic factor from the intestine for a time. No effect that is appreciable from laboratory studies beyond a bacteriostatic one can be demonstrated by sulfanilamide on the streptococci or other bacteria resident in the bowel, although it is possible that such may take place to slight and temporary degrees. No observations were made on the control of systemic infections by sulfanilamide drugs in the blood stream. Up to the present it has been proven that they are practically ineffective in ulcerative endocarditis in rendering the blood stream negative.

Sulfaguanidine was not used. The experience with these drugs suggested that one cannot deduct as to which one of the preparations would be best to employ. When benefit takes place from them, it seems to be about the same, whether one uses sulfanilamide, sulfapyridine or sulfathiazole. It was slightly suggested that sulfanilamide seemed to be the better form in *C. welchii*, hemolytic and the green streptococci, and sulfathiazole in the inimical form of *E. coli*, aërogenes, pyocyaneous and streptococcus infections of the bowel.

The ordinarily employed different vitamin preparations were not encouraging in results although vitamins were more or less employed in all the cases. Five cases of chronic arthritis were intensively treated with large doses of vitamin D (Estron) without benefit. The most benefit seemed to come from the various B complex preparations providing the doses are ample, kept up for months, and especially if the preparation had a laxative effect on the patient.

The writer desires to report 337 instances of chronic arthritis observed by him from 1923 to the present. For the purpose of eliminating the generally recognized factors were treated for various lengths of time, and those that were unimproved were examined and treated by biotoxic measures.

Summary and Conclusions. Intestinal organisms are more or less frequently passing into the general blood stream, probably by way of the peritoneal lymphatics. The human intestinal canal, even in apparent health, contains many forms of streptococci, potentially pathogenic in the circulation. Under conditions of symbiosis with certain other organisms in the intestine, these streptococci can become pathogenic. Organisms may appear in the blood stream in unusual types when they are still the original forms. Gaining the circulation, streptococci may lodge in the cancellous tissue of the bone under the joint bone or surfaces and in the periarticular and fascial structures causing an initial infection. These tissues then may become sensitized to them, and as more streptococci, and perhaps some of the mixed infection types, are added to the circulation, a remissive, progressive change in the joints or bones ensues. These primary and reinfective factors from the intestine have not received the attention they deserve in the subject of chronic arthritis. While the use of streptococci vaccines may be of value, they are not efficient in controlling the infection in the intestine. In most instances attack on the associated infections by biologic and dietetic means controls the streptococcic infection, this being important on the parasitic character of the streptococci within the bowel as well as those that gain the blood stream.

A method of biologic and dietetic treatment for chronic arthritis is suggested. The results of handling 337 cases of chronic arthritis, 205 of which, by gastro-intestinal treatments, are presented. Of the latter, about 17% having treatment for the various well-known

digestive disorders causing secondary biotoxic states showed improvement. In 181 cases of primary biotoxic intestinal conditions practically 68.5% showed marked improvements in reduction of swelling, usefulness of joints and control of remissions, and about 26.5% more were distinctly improved, there being about 9.2% of failures, these latter being old cases with much deformity.

A reasonable conclusion from these results is, that, while other causes than intestinal have importance in chronic arthritis, significant etiologic and therapeutic factors are contained in the digestive tract, and of these, infections of intestinal origin comprise an important group.

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THE AMOUNT OF IODINE IN THE BLOOD AND URINE IN PATIENTS WITH DIABETES INSIPIDUS.

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Recently, Blotner and Cutler[2] reported certain observations on the effect of total thyroidectomy in 3 patients with diabetes insipidus who were observed for 5 years following operation. Total thyroidectomy relieved the excessive urinary excretion of the diabetes insipidus in 2 cases, while no effect was noted in the other case. However, in the latter case it was felt the patient had accessory thyroid tissue because of her normal metabolism and lack of signs and symptoms of myxedema. The administration of thyroid extract reëstablished the polyuria and polydipsia in the 2 cases. Histologic studies of the thyroid gland in 2 of the cases indicated a small degree of hyperactivity. The above observations indicated that the thyroid gland played some rôle in the physiologic aspects of diabetes insipidus.

Since there appeared to be a relationship between thyroid activity and water balance in patients with diabetes insipidus, it seemed reasonable that this association could be more firmly established by observing the level of iodine in the blood and the excretion of iodine in the urine in a group of patients with diabetes insipidus. This paper deals with the results of the blood and urine iodine studies in 15 patients with diabetes insipidus.

Iodine is a normal constituent of human blood and urine. The values for the concentration of iodine in the blood vary somewhat

according to the method used. Nevertheless, in adhering to a standard procedure for determining iodine, results can be obtained which are relative one to another. Perkin and Lahey[12b] have used an open combustion method as described by Perkin[9b] in 25,000 analyses of blood iodine and found it to be satisfactory for clinical and research purposes. In persons without clinical evidence of thyrotoxicosis, they found that the average or mean level of iodine in the blood was 6.8 micrograms per 100 gm. with no significant variations attributable to age, sex or season. Curtis and Puppel[3a] found that the normal person excreted in the 24-hour daily urine from .007 to .196 mg. of iodine or an average of .051 mg. and that there did not appear to be any relation between the amount of iodine in the urine and the volume of urine excreted. In the Boston district, Perkin found the daily urine excretion of iodine to range from .060 to .140 mg. with mean values of .090 to .110 mg. These values, however, may be influenced by the daily regimen.

There have been reported minor physiologic variations of the blood iodine level during the menstrual cycle,[15] during pregnancy,[7] seasonal variations[4,8] and during exercise.[6] These variations in the blood iodine level may or may not extend beyond the normal range for the method used. Elevation of blood iodine has been observed in patients with diseases of the liver and of the biliary passages,[10] in leukemia[4] and in the early stages of acromegaly.[12b] However, the greatest variation from the normal appears in patients with hyperthyroidism. In this disease there usually occurs a considerable increase in the blood iodine level and a marked increase in the excretion of iodine in the urine. In hyperthyroidism, Perkin and Lahey[12b] found that the average and mean values for blood iodine were 15.5 and 11 micrograms per 100 gm., respectively. These same workers[12c] found the urinary iodine excretion of these patients to average .110 to .225 mg. per 24 hours with a maximum of .410 mg. In the urine of cases with hyperthyroidism, Curtis and Puppel[3b] found a daily excretion of iodine ranging from .013 to .954 mg. with averages ranging from .030 to .595 mg.

Plan of Investigation. The work reported here was carried on according to the following methods. The iodine in the blood and urine was determined during and after a course of pituitrin therapy in a group of cases with diabetes insipidus. In the cases studied during the period of treatment with pituitrin, 1 cc. of obstetric pituitrin was taken three or four times a day intranasally or subcutaneously for from 1 to 10 weeks when the polydipsia and polyuria were well controlled before the tests were made. When the tests were made after pituitrin was omitted, a period of from one week or more elapsed after the discontinuance of pituitrin therapy, at which time the patients were drinking and passing huge volumes of fluid. The concentration of the total iodine in the blood was studied in some specimens taken before breakfast, in others, during the day. The determinations of the total blood iodine were made in duplicate, using 20 cc. samples of venous blood according to the method described by Perkin.[9b] In addition, the organic and inorganic iodine fractions in the blood were determined in 11 of

the cases. The tests for iodine in the urine were made on 24-hour samples of urine obtained immediately either before or after the blood was obtained. The patients were instructed to follow their usual diet and the specimens were not taken when they had a sea fish meal which might reflect an increased amount of iodine in the blood and urine. One patient was observed in the hospital for 20 days when the fasting blood iodine and the 24-hour excretion of iodine in the urine were determined daily during periods with and without pituitrin injection.

Iodine tolerance tests were observed in 3 cases with and without pituitrin therapy. At least 4 weeks elapsed between tests. A standard dose of .6 cc. of compound solution of iodine (Lugol's solution) U. S. P. in a glass of milk was employed. The concentration of the blood iodine was determined in specimens taken during fasting and at intervals of 30, 60, 90 and 150 minutes after the ingestion of the iodine. The total amount of iodine was determined in the urine excreted during the 24 hours following the ingestion of the iodine in one case.

The total amount of iodine was determined in the thyroid glands of 2 thyroidectomized patients with diabetes insipidus and the results were compared with those obtained in 2 normal thyroid glands which were removed for the treatment of heart failure without hyperthyroidism.

Clinical Material. The group studied comprised 10 males and 5 females with diabetes insipidus who had the disease for a number of years. Their ages ranged from 11 years to 69 years, although the majority were between 20 and 30 years old. Their weights were about normal or somewhat below normal for their height, age and sex, but one patient was obese, weighing 205 pounds. The criteria for the diagnosis of diabetes insipidus were a persistent daily fluid intake and output of about 8 to 14 liters for years, which were reduced to normal following the intranasal or intramuscular administration of pituitrin. The disease was of idiopathic origin in 12 cases, of postencephalitic origin in 2 cases and due to a pineal tumor in one case. Two cases were relieved of their polyuria and polydipsia by total thyroidectomy about 4 years before the iodine tests were made. The various laboratory data were not remarkable except that the fasting blood cholesterol was elevated in some cases, not merely in the thyroidectomized patients, and usually showed a marked rise after a fat meal.[1] The basal metabolism ranged from +8 to −18%. In the 2 thyroidectomized patients, the basal metabolism was about −25%.

Results. The results of the total blood iodine level and of the total iodine excretion in the 24-hour daily urine in 12 cases of idiopathic origin are given in Table 1. These findings show that when no pituitrin was administered, the blood iodine was usually at a low normal level, although in one specimen it was elevated, being 12.6 micrograms per 100 cc. The average was 5.5 micrograms per 100 cc. In comparison, the average or mean blood iodine in normal people was 6.8 micrograms per 100 cc. with a range of from 3 to 10 micrograms with the method used.

The 24-hour urine showed varying amounts of iodine and in most instances, the iodine excretion was markedly increased. The average 24-hour urine iodine was .339 mg. and the average daily urine volume was approximately 10 liters.

When pituitrin was administered, the results were opposite to those when no pituitrin was given. In this instance, the blood iodine level was increased in most cases, the average being 9.8 micrograms

per 100 cc. The 24-hour urine excretion of iodine decreased considerably, the average being .177 mg. and the average daily urine volume was approximately 3 liters. A summary of these results is given in Table 2.

TABLE 1.—TOTAL IODINE IN THE BLOOD AND URINE OF 12 PATIENTS WITH DIABETES INSIPIDUS.

	No pituitrin.			*On pituitrin.*		
Case No.	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
1	3.0	.318	10,630	4.3	.079	960
2	5.6	.201	7,440	17.0	.125	2120
	3.6	.217	10,320			
3	7.0	.208	4,900	9.2	.143	1350
	6.7	.108	6,500	12.0	.078	1400
4	12.6	..	..	4.2		
	8.0	.936	9,360	6.8	.173	3840
5	3.2	.345	11,520	17.8	.127	5760
		.028	9,450	6.5	.168	2400
	7.8	.147	10,500	7.8	.097	2850
	6.5	.030	9,600			
6	3.5					
	5.2	.288	11,520	8.4	.300	4800
	4.5					
7	5.5	.202	8,400	10.5	.185	2160
		.207	8,640	..	.105	2400
8	4.6	.181	12,960	13.4	.323	3480
9	5.0	.749	12,480	7.0	.317	5280
		.352	8,160	6.5	.196	4950
	9.2	.134	6,720			
10	3.4	.235	8,400			
11	..	.797	9,360	9.8	.182	2120
	5.7	.598	11,520	9.9		
12	..	..	..	4.8	.147	1750
				13.2	.466	1150

TABLE 2.—TOTAL IODINE IN BLOOD AND URINE IN 12 PATIENTS WITH DIABETES INSIPIDUS.

	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
	No Pituitrin.		
Average	5.8	.319	9460
Range	3.0–12.6	.028–.936	
	On Pituitrin.		
Average	9.4	.189	2860
Range	4.2–17.8	.078–.466	

An analysis of these findings suggests that in an untreated case of diabetes insipidus, there was an increased excretion of iodine in the urine and an associated low normal level of iodine in the blood. In contrast, when these patients were treated with pituitrin the opposite occurred. The excretion of iodine in the urine was diminished and the blood iodine level was increased.

In a case with diabetes insipidus and pineal tumor given pituitrin and Roentgen-ray therapy, the blood iodine level was low and there

was some increase in the iodine excretion in the urine, as shown in Table 3. Roentgen-ray therapy may have been a factor in the results of this case.

TABLE 3.—IODINE IN THE BLOOD AND URINE OF A PATIENT WITH DIABETES INSIPIDUS AND PINEAL TUMOR.

	On pituitrin.		
Case No.	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
15	3.2	.201	2100

In the 2 patients with diabetes insipidus who were relieved of their polyuria and polydipsia following total thyroidectomy, the blood iodine levels were low, ranging from 1.5 to 4.8 micrograms per 100 cc., and the excretion of iodine in the urine was normal. These results were comparable to those obtained in myxedema, as shown in Table 4. In the usual case of myxedema, the average blood iodine level is 3.5 micrograms per 100 cc. with the method employed.

TABLE 4.—TOTAL IODINE IN THE BLOOD AND URINE OF 2 PATIENTS WITH DIABETES INSIPIDUS 4 YEARS AFTER TOTAL THYROIDECTOMY.

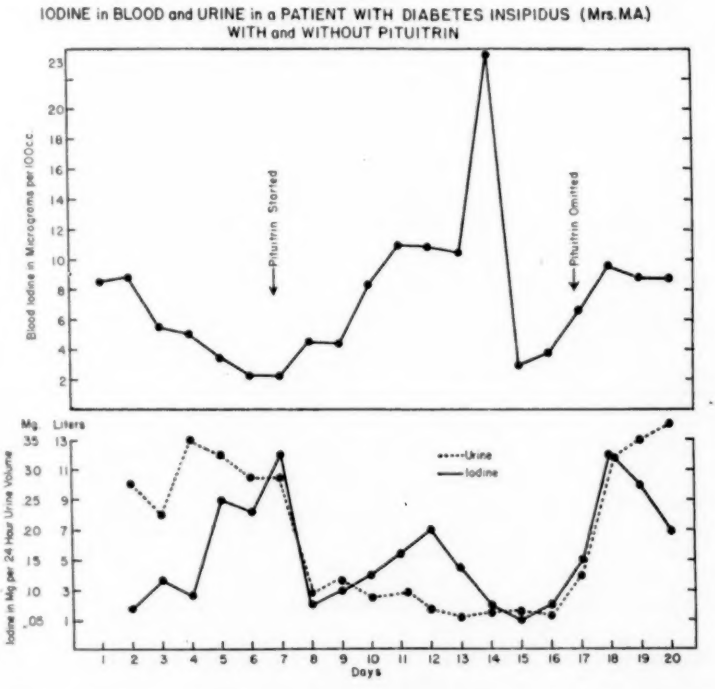
	No pituitrin.		
Case No.	Blood iodine, mcg. per 100 cc.	24-hour urine, iodine, mg.	24-hour urine, volume, cc.
13	3.4	.152	4000
14	4.8	.150	2500
	1.5	.094	3300
	3.6		
	4.0	.071	2150
	2.4		
	4.0		

One patient was admitted to the hospital for observation for 20 days. The iodine was determined daily on fasting samples of blood and on 24-hour specimens of urine in order to study the iodine on consecutive days over a period of time. The patient was given a house diet which contained about .150 mg. iodine daily.

The patient took no pituitrin for 2 weeks before admission to the hospital and her daily urine output approximated 10 liters. The results of her iodine studies are given in Chart 1. During the first 7 days in the hospital, no pituitrin was administered and her urine volume varied from 8 to 13 liters. During this period the blood iodine level was at first normal and then decreased to a low level while the urine iodine excretion was at first low and then increased considerably. For the next 10 days pituitrin was injected so that the daily urine volume varied from 2500 to 1200 cc. During this period the iodine excretion in the urine decreased and became low while the blood iodine level increased markedly. These blood iodine results were not fortuitous because the organic and inorganic iodine fractions were determined also and they amounted to the total

blood iodine concentration. However, on the last 3 days of this period, the blood iodine dropped to a very low level. Finally, pituitrin was omitted again for 3 days and the urine volume ranged from 12 to 14 liters; the iodine excretion increased again and the blood iodine remained at a high normal level for 3 days, the final period of observation.

CHART I



The iodine content of pituitrin was determined to ascertain whether it contained appreciable amounts of iodine. The iodine concentration was found to be .080 mg. per 100 cc. pituitrin. This amount was considered insufficient to influence blood and urine results.

Blood Iodine Fractions. The fractionation of the iodine of the blood was carried out in 11 cases by methods reported elsewhere.[11] This was done in an endeavor to find if the proportion of organic to inorganic iodine in the blood of patients with diabetes insipidus was different from that found in normal individuals and in patients with hyperthyroidism and with myxedema. The approximate proportions of organic to inorganic iodine are 65 to 35 in the normal; 55 to 45 in hyperthyroidism; and 40 to 60 in myxedema with the methods used. In this connection, the results of this study indicated that the relationship of the organic to inorganic blood iodine was not con-

sidered to be abnormal in these cases for their total blood iodine level, whether or not pituitrin was administered (see Table 5). In a few of the cases, the normal relation of the organic and inorganic iodine was reversed. The significance of this is not apparent. Since both the organic and inorganic blood iodine fractions were determined independently of the total blood iodine, it will be noted that the sum of the fractional analyses did not always equal the total. In most instances, however, the results are within the limits of experimental error for methods of blood iodine analyses.

TABLE 5.—TOTAL BLOOD IODINE AND ITS FRACTIONS IN 11 PATIENTS WITH DIABETES INSIPIDUS.*

	Pituitrin.			*No pituitrin.*		
Case No.	Total blood iodine, mcg. per 100 cc.	Iodine, organic, ethyl alc., mcg. per 100 cc.	Iodine, inorganic, mcg. per 100 cc.	Total blood iodine, mcg. per 100 cc.	Iodine, organic, ethyl alc., mcg. per 100 cc.	Iodine, inorganic, mcg. per 100 cc.
1	4.3	4.0	0.0	3.0	3.1	0.0
2	17.0	14.6	2.2	3.6	3.3	
3	12.0	5.0	7.2	7.0	7.5	
4	6.8	7.1	1.8			
5	6.5	6.4	..	7.8	6.1	2.4
	7.8	5.0	2.2			
6	..	..	..	4.5	4.2	
7	10.5	2.6	7.4	5.5	5.3	1.3
8	..	..	..	5.2	4.5	2.2
9	6.5	3.3	5.5	9.2	4.0	6.1
	4.4	4.2	2.2	8.8	2.5	5.1
	8.4	5.8	3.0	5.2	2.0	2.9
	11.0	6.7	4.3	9.6	4.7	5.0
	23.2	15.6	8.4	8.6	6.5	2.2
13	..	..	..	3.4	0.0	3.5
14	..	..	..	4.0	3.1	2.4

* Cases 13 and 14 had total thyroidectomies performed 4 years previously.

Iodine in Thyroid Glands. From the foregoing observations, there appeared to be an increased excretion of iodine in the urine of patients with diabetes insipidus. Consequently, it seemed of interest to determine whether the iodine content of the thyroid gland in diabetes insipidus was diminished by the increased excretion of iodine in the urine. As the result, the total quantity of iodine was determined in the thyroid glands of 2 patients with this disease who had had these glands removed previously. As control tests, the iodine was determined in the normal thyroid glands of 2 cardiac patients who had total thyroidectomies for the relief of cardiac decompensation. These results are given in Table 6. In the patients with diabetes insipidus, there was .402 mg. of iodine per gm. of wet tissue and the total amount of iodine in the whole thyroid glands was 6.96 mg. and 8.22 mg. In the control thyroid glands, there was .605 mg. and .500 mg. iodine per gm. of wet tissue and the whole of these glands contained 11.1 mg. and 15.0 mg., respectively. These results suggest that there is a decreased amount of iodine in the

thyroid gland of patients with diabetes insipidus. Nevertheless, it must be remembered that this is a small series.

TABLE 6.—IODINE IN THYROID GLANDS OF 2 PATIENTS WITH DIABETES INSIPIDUS COMPARED WITH 2 CONTROL THYROIDS.

Case No.	Iodine per gm. wet tissue, mg.	Iodine in whole thyroid gland, mg.
Diabetes Insipidus.		
A	.402	6.96
B	.402	8.22
Cardiac Controls.		
1	.605	11.07
2	.500	15.01

Iodine Tolerance Tests. Iodine tolerance tests were made in 3 cases in order to determine whether the thyroid gland has an extra affinity for iodine similar to the hyperplastic thyroid gland of patients with exophthalmic goiter. The results are given in Table 7. Perkin, Brown and Lang[12,13] and Fitz and Hunt[5] have shown by means of these tests that when persons with hyperthyroidism are given a specific amount of iodine, the iodine in the blood does not rise as high as in normal persons and returns to the basal level more rapidly. In contrast, when patients with thyroid deficiency are given iodine intravenously, the blood iodine rises to higher levels than normal and falls more slowly to the basal level and a greater amount of iodine is recovered in the urine.

TABLE 7.—IODINE TOLERANCE TESTS IN 3 PATIENTS WITH DIABETES INSIPIDUS.

Case No.	Hours after iodine test meal.	*No pituitrin.* Blood iodine, mcg. per 100 cc.	*Pituitrin.* Blood iodine, mcg. per 100 cc.
5	0	9	7
	½	275	84
	1	355	57
	1½	274	38
	2½	262	56
6	0	6	
	½	93	
	1	134	
	1½	69	
	2	109	
3	0	6	7
	½	248	230
	1	203	200
	1½	165	163
	2	158	174
Urine, iodine*		48 mg.	25 mg.
Urine, volume		1950 cc.	5900 cc.

* Total iodine excreted in urine during the 24 hours after ingestion of iodine.

In Case 5 when pituitrin was given (see Table 7), the blood iodine curve was much lower than normal and like that observed in hyperthyroidism. When no pituitrin was given, the blood iodine level was more than twice as high as that found in normal people.

In Case 6, the blood iodine curve was normal without pituitrin. In Case 3, the blood iodine curves with and without pituitrin were much the same but about twice as high as normal. However, with pituitrin 25 mg. of iodine was excreted in the urine during the 24 hours after the ingestion of iodine, compared with 48 mg. of iodine when no pituitrin was being administered.

Discussion. The data in this study reveal that in untreated patients with diabetes insipidus there is an increased excretion of iodine in the urine and usually relatively low normal blood iodine levels. It is suggested that the most likely cause for these changes is a washing-out process resulting from the exchange of huge volumes of fluid in these patients and the failure of reabsorption by the kidney. When pituitrin is administered, the blood and urine iodine results are reversed and the fluid intake and output are markedly decreased because of the effect of pituitrin on renal function which increases reabsorption. This idea may be strengthened by the fact that pituitrin diminishes the excretion of iodine in the urine after the ingestion of Lugol's solution. Furthermore, Perkin[9a] has found high blood iodine levels in patients with chronic nephritis with marked renal insufficiency and edema which indicates a retention of iodine. Diodrast clearance tests[16] made in some of these patients also suggest that pituitrin diminishes the excretion of iodine. Salter[14] believes that the high iodine turnover in these cases may be a washing-out phenomenon like that seen with urea. On the other hand, the possibility of a thyro-pituitary relationship as a cause of these findings should be considered.

Summary. This paper presents a study of the iodine in the blood and urine of 15 patients with diabetes insipidus. In addition, the amount of iodine was determined in the thyroid glands of 2 of these patients who had had a total thyroidectomy.

When the patients were not treated and there were marked polydipsia and polyuria, the average blood iodine was 5.8 micrograms per 100 cc. (range, 3.0 to 12.6). The average 24-hour excretion of iodine in the urine was .319 mg. (range, .028 to .936 mg.). In contrast, when pituitrin was administered, the average blood iodine was 9.4 micrograms per 100 cc. (range, 4.2 to 17.8 micrograms). The average 24-hour excretion of iodine in the urine was .189 mg. (range, .078 to .466 mg.). The relation of the organic to the inorganic blood iodine was considered to be practically normal in these cases. The iodine content of the two thyroid glands was decreased compared with two control thyroid glands.

In untreated patients with diabetes insipidus, there appears to be an increased excretion of iodine in the urine and usually relatively low normal blood iodine levels. When pituitrin is administered, the excretion of iodine in the urine diminishes and the blood iodine level increases. These findings may represent a failure of reabsorption of iodine by the kidney which is altered by pituitrin administration.

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STUDIES OF THE EXPECTORANT ACTION OF IODIDES.*

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The clinical use of the expectorant group of drugs is widespread but their use is predicated purely upon an empirical basis. The little that is actually known of the mode of action of these agents has been derived from clinical experience in the treatment of respiratory diseases, both infectious and allergic in character. Our interest in expectorants arose some time ago in attempting to find a drug which would be most effective in liquefying the extremely viscid secretions of the asthmatic patient, especially of the chronic type or of those in status asthmaticus.

Search of the literature revealed a definite lack of data concerning the mechanism by which expectorants produce their effects. The earliest attempts to prove that expectorant drugs actually were effective were carried out with ammonium compounds and were performed at first in animals. However, Coleman[1] in 1916 observed the effects of ammonium compounds in 7 human cases of bronchitis and showed by rather crude methods that the drug was excreted in the sputum as indicated by an increase in the ammonia N.

* Read before the meeting of the Association for the Study of Allergy, New York, June, 1940.

More recent work with expectorants, especially that carried out in animals by Gordonoff and his coworkers abroad, has made it possible to classify these drugs on a more logical basis. From these experiments, Gordonoff[2] concluded that the action of expectorants depends upon the predominance of one of two factors: 1, stimulation of the smooth musculature of the bronchi, termed the *excretomotor* action of the drug, which is either a manifestation of increased bronchial peristalsis or a wavelike motion dependent entirely upon the movement during the respiratory act; and 2, liquefaction of the bronchial secretions by actual excretion of the drug into the bronchi and subsequent delay in resorption of these secretions, which is called *secretolysis*. Drugs belonging to the excretomotor group include ammonium chloride, guaiacol, thymol and ether. In the secretolytic group are: iodides, saponin, sugars and sulphur. Gordonoff concluded that efficient respiration is essential for the action of any expectorant and that the expectorant to be used in a specific case should be chosen according to the type of secretion already present; that is, it should be secretolytic if the secretion is scanty and excretomotor if it is fluid and abundant. He feels that sedatives do more harm than good, as they depress respiration and cancel the effect of good respiratory movement upon the expectorant action of the drug.

It was evident, therefore, from a review of the literature that nearly all the evidence as to the action of expectorants was based upon the results of animal experiments. It occurred to us that it might be possible to study the expectorant action of various drugs in the human with the aid of the bronchoscope. Our plan was to administer the drug to be studied either parenterally or orally and then to aspirate the bronchial secretions by the bronchoscope. The condition of the bronchial mucosa was to be observed during the process, if at all feasible. The secretions thus obtained then were to be studied chemically for the presence of ions not usually or normally detectable. This was the general plan adopted although certain departures from it were necessary, as when the drug was given orally. It was decided to start with the iodides since a simple test was available for the detection of the iodide ion.

Review of the literature as to the effect of iodides indicated that the iodides render colloids more soluble and less viscid *in vitro*, although Sollman[5] doubts whether this actually is the case in the concentration reached therapeutically. There is evidence of iodides being excreted into the saliva and urine but not into the bronchial secretions in humans, although Stieglitz[6] by postmortem staining methods showed the presence of the iodide ion in the bronchial mucosal cells as well as in other parenchymatous secreting cells. As previously noted, iodides are believed to belong to the secretolytic group. Thus Gordonoff and Merz[4] showed that iodides will decrease the density of a contrast medium introduced into the bronchi of rabbits. Gordonoff and Lehmann[3] also were able to show

a delay in absorption of a sugar solution introduced into the bronchi of rabbits. From these experiments the conclusion was reached that the action of iodides is mainly due to excretion into the bronchial tree, with subsequent delay in resorption of the secretions already present. The latter actions thus make the respiratory act and the coughing mechanism more effective in raising these secretions. The motor stimulation noticeable with ammonium chloride was almost entirely lacking in iodide administration. These conclusions were arrived at by inference from the experimental data, since the actual presence of iodides was not demonstrated nor was any information obtained as to how soon the iodides appear in the bronchial secretions or how long it remains; also whether there was any difference noted when the drug was given by mouth as contrasted with intravenous injection. It was known, however, that iodides were readily absorbed from the gastro-intestinal tract, being given usually in the form of potassium iodide in doses of 4 to 8 gm. The usual intravenous dose was 1 to 2 gm., although up to 10 gm. could be safely given. It was decided to carry out the initial experiments with the iodide being given intravenously and to compare it subsequently with the oral route.

Procedure. Our first experiments were carried out in dogs but without success, since satisfactory data could not be obtained. We, therefore, discarded attempts at further animal experimentation and proceeded at once to experiment in the human. The patients utilized were patients from the allergy or bronchoscopic departments who had either asthma, bronchiectasis or other pulmonary conditions requiring bronchoscopic examination or treatment. The general procedure followed in each case consisted first in the insertion of the bronchoscope and the aspiration of a control specimen of secretion into the special glass containers utilized for that purpose. Sodium iodide was then injected intravenously in doses of 15 to 31 grains. Following the injection, specimens of the secretions were withdrawn in like manner at 5-minute intervals for the duration of the time it was feasible to retain the bronchoscope. The specimens thus obtained were then tested in the laboratory for the presence of iodides. The method used was a purely qualitative one but was sufficiently sensitive to detect very minute amounts of iodides as determined by preliminary control tests. The procedure was briefly as follows: Organic matter was destroyed by heating the material to be treated with a strong solution of potassium hydroxide in a tube or crucible. It was then extracted with water and the extract tested for the presence of iodine by the addition of a starch solution. A definite blue color was taken as positive (+), faint blue as doubtful (±) and absence of color as negative (−).

In order to obtain information as to the excretion of the iodides through other channels, in 4 patients specimens of saliva were aspirated into a separate container at the same time that the bronchoscopic specimens were collected. These were likewise examined

for iodides in the same manner as the bronchial secretion and the appearance time noted. Urine specimens also were collected by 4 patients, both before and at intervals after the iodide injection and examined by direct test for iodides.

Having determined the approximate appearance time of the iodides in the bronchial secretion after intravenous injection and its probable persistence, we next attempted to determine the appearance time after oral ingestion. Accordingly, a group of 9 bronchoscopic patients were given 60 grains of potassium iodide contained in 1 dram of an aqueous solution orally immediately prior to bronchoscopic examination. The time at which the first specimen was aspirated was noted and one or in some instances two specimens of secretion were aspirated in similar manner as in the intravenous group. These were then examined for iodides. Aspiration of repeated specimens at 5-minute intervals was not deemed necessary in this group, as we were interested only in the appearance time in comparison with that of intravenous group.

Results. The results of the experiments in the group given the iodides intravenously are shown in the following chart:

CHART 1.—EXCRETION OF IODIDE AFTER ITS INTRAVENOUS INJECTION.

Bronchial Secretion.

Case and amount.	Control.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	Urine.		Saliva pos. at.
									Neg.	Pos.	
Mr. W. 30 gr.	0	0	±	+	+	+					
Mr. F. 15 gr.	0	±	±	+	+	+					
Mr. F. 30 gr.	0	0	±	+	+	+	+	±	45″	1′ 30″	
Mr. L. 30 gr.	0	0	+	+	+	+			50″	1′ 30″ 2′ 0″ 5′ 0″	10–30 mm.
Mr. J. 15 gr.	0	0	0	+	+	+	0	0	1′ 15″	1′ 55″ 4′ 40″	20–40 mm.
Mr. L. 31 gr.	0			0	+	+	+	+			20–40 min.
Mr. S. 31 gr.	0	0	+	+	+	0			1′ 0″	1′ 30″ 3′ 0″	10–30 min.

It will be noted that while a trace of the iodide was detectable in 1 patient after 10 minutes, it was a little more pronounced at 15 minutes, definite at 20 minutes in all but 1 instance and definite in all cases at 25 minutes. In the 2 cases receiving only 15 gr., little difference was noted from those receiving twice as much; in fact, in Mr. F., who received 15 gr. on one occasion and 30 gr. on another, little difference was observed. This might be taken to indicate that the quantity injected has little or no effect upon the appearance time.

The bronchoscope could not be retained long enough in every patient to determine the time at which the iodides disappeared from the bronchial secretion. In one instance (Mr. S.) it was no longer evident at 30 minutes, in another (Mr. J.) at 35 minutes and in a third (Mr. F.), only a trace was present at 40 minutes. It is interesting to note that no evidence of the iodide was present in the urine of these 3 patients examined at 60-minute, 75-minute and 45-minute intervals respectively, but did appear subsequently. In a fourth patient (Mr. L.) the urine was negative at 50 minutes but was positive at 90 minutes. This might be taken to indicate that the iodide present in the bronchial secretion first is resorbed into the blood and then is excreted into the urine by the kidney, rather than being immediately excreted by the kidney.

In the 4 patients in whom salivary studies were carried out, the iodides first appeared in 10 minutes in 2, and in 20 minutes in the other 2. This corresponded roughly to the time of appearance in the bronchial secretions, with possibly a little earlier appearance for the salivary group.

It was difficult under the conditions of the experiments to determine whether the amount of bronchial secretion was increased by the iodides or to detect any changes in the bronchial mucosa as compared to that preceding the iodide injection. While attempts were made to determine these facts, no significant conclusions could be drawn.

CHART 2.—EXCRETION OF IODIDE AFTER ITS ORAL INGESTION.

Case.	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.
Mr. F.	0							
Mr. S.	0							
Mr. O.			+					
Mr. A.			0	*				
Mr. G.				+				
Mr. T.						+		
Mr. S.						0		
Miss D.						+	+	
Mr. R.								0

All patients received f℥j sat. solution of pot. iodide.

The results of the experiments in the group who received the iodides orally are shown in Chart 2. As in the intravenous group, the iodides appeared in the bronchial secretions of 3 patients in 15 to 20 minutes and at longer intervals in the others. While this

may be taken to indicate a somewhat slower excretion after oral administration, this conclusion cannot be made definitely because of the conditions of the experiment. Nevertheless, the primary purpose of the experiment, namely, that iodides appear in the bronchial secretion after oral administration was fulfilled by these experiments.

Comment. The results obtained indicate that iodides are excreted into the bronchial tree from the blood. The time taken before this excretion occurs is somewhat variable, but it takes place within 15 to 25 minutes after intravenous injection. The excretion probably is a little slower when given orally than when given intravenously, but this difference could not be definitely determined and is not significant in clinical application. The intravenous administration offers no important advantage over the oral method, especially in view of the added work entailed in its use. The salivary excretion of iodides occurs promptly, although it is hard to determine under the conditions of the experiment, but urinary excretion is delayed. This may be taken to indicate that the salivary glands and bronchi act as the selective excretory organs for this drug and that urinary excretion must await resorption from the bronchi and gastro-intestinal tract. This is similar therefore to Gordonoff's findings in the experimental animal.

Conclusion. We have been able to demonstrate for the first time at least in the human that iodides given either orally or intravenously are excreted into the bronchial secretion within 15 to 25 minutes. We believe that this excretion probably accounts for the action of iodides as expectorants and that oral administration probably is just as effective as intravenous and less troublesome.

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THE DIAGNOSTIC VALUE OF THE TAKATA–ARA REACTION.

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Since the introduction of the Takata-Ara reaction in 1925 a considerable amount of literature has accumulated on the subject. This has been thoroughly reviewed by Magath,[2] Wayburn and

Cherry,[5] and others. Two facts stand out conspicuously from such reviews: first, that we are still ignorant of the mechanism of the reaction; and, second, that a marked difference of opinion exists as to its diagnostic value. This difference would appear to be due to lack both of uniformity in the technique employed and of precision in reading the results of the reaction. In an effort to contribute something toward settling the question of the value of the test, we have recently reviewed a series of cases on which the reaction was performed and the results of our investigation are given below.

No detailed historical sketch of the Takata-Ara reaction will be attempted. Suffice it to mention that the test was described in 1925 by Takata[3,4] and Ara[4] for the study of four widely separate diseases, namely, syphilis, meningitis, pneumonia and tuberculosis, and that Jezlar[7] in 1929 modified the technique and used the test as a diagnostic measure for cirrhosis of the liver. Since this time many American, English, German, French and Italian workers have reported their findings on a variety of different lesions, using various modifications of a basically similar technique. Most of the interest in the test has throughout been in its merits as a diagnostic measure in hepatic cirrhosis.

The mechanism of the Takata-Ara reaction, much discussed, remains obscure. It is even uncertain whether flocculation occurs because of the absence from positively reacting plasmas of some protein normally exerting a "protective colloid" effect or because of the presence in such plasmas of a protein or other substance exceptionally apt to form precipitating complexes with the mercuric reagent. In this regard it is of interest that no flocculation occurs when saline is substituted for plasma in performing this test. In any case our own observations lead us to believe that positive reactions are not due either to mere abnormalities of the A/G ratio because of lowered albumin content or to the presence of increased fibrinogen, as Wuhrmann and Leuthardt[6] have suggested. On the other hand, as regards absolute increase in the plasma globulins, in this institution where plasma protein determinations are done by the salting-out method, figures are available on 10 of the 23 positive or plus-minus reactors analyzed below. In all but 1 an actual increase in the plasma globulins was found. The question of the separation of these globulins has undergone a metamorphosis in the past few years and is still in some debate. However, it is of interest that more recent techniques[1] indicate an increase in the beta-globulin fraction in cases of cirrhosis of the liver.

Technique. A great deal of the discrepancy that has arisen in the evaluation of the Takata-Ara test is apparently due to differences in the methods employed in carrying out the reaction and in reading and interpreting the results. For this reason, a detailed description of the method that we have been using for some time is included in this article.

The test may be done on blood serum, plasma, or transudates, such as ascitic fluid. Most of our results were obtained from oxalated plasma

procured at the time of carrying out a complete hemogram. Blood is usually taken for such tests in the morning, between 10 and 12 o'clock to avoid any effect of digestive processes on the plasma. At least, 1 cc. free from hemolysis and cells, is required.

A series of 8 tubes, approximately 10 cm. in length and inner bore of 1 cm., are placed in a rack. The tubes must, of course, be thoroughly clean. One cubic centimeter of 0.9% NaCl is pipetted into each tube and 1 cc. of plasma added to the first tube. This is mixed with the saline by shaking and 1 cc. of the mixture withdrawn and placed in the second tube. By continuing in this manner and discarding 1 cc. from the last tube a series of increasing dilutions ($\frac{1}{2}$ to $\frac{1}{256}$) of plasma in saline is set up. To each tube first 0.25 cc. of a 10% solution of sodium carbonate and then 0.15 cc. of 0.5% bichloride of mercury are added. Complete mixing is obtained by shaking after each solution has been placed in the tube. A slight precipitate, which disappears on shaking, may occur after addition of the mercury. The series of tubes is then allowed to stand at room temperature for 24 hours.

At the end of this interval, the result of the test is read by estimating the amount of precipitate in each tube. This is expressed as 0, T (Trace), 1, 2, 3 or 4. Precipitates classed as "4" occupy approximately the lower third of the solution in the tube. In doubtful cases, accurate reading of the amount of precipitate may be accomplished by thoroughly shaking up the tube and filling a Wintrobe sedimentation tube to the 10-cm. mark with a portion of the contents. The Wintrobe tube is then centrifugalized at high speed for 15 minutes. Less than 1 mm. of whitish sediment in the bottom of the tube is classed as a trace (T), 1 to 2 mm. as "1," 2 to 3 mm. as "2," and so on. Any amount over 4 mm. is designated "4."

The Takata-Ara reaction is positive when two adjacent tubes show a Grade "4" degree of precipitate and the next tube is at least a Grade "3," for example (00T24441) or (00134421). Plus-minus reactions are reported whenever the criteria for the positive reaction are not reached, but at least two tubes show a Grade "3" sediment, for example (00T12431), (0001331) or (000TT332). All reactions of lower degree are negative as (000TT231) or (000TT1TT). It would appear from an analysis of our findings that accurate reading of the reaction is extremely important.

Analysis of Results. The present study covers an analysis of 300 consecutive tests carried out in our laboratory using the technique described above. Most of them were done on oxalated plasma obtained at the time of doing a complete morphologic blood study on cases where a hyperbilirubinemia was present or in which there was some reason to at least suspect the presence of hepatic disease. Using the criteria of reading the reaction given above, 277 cases are to be classified as negative, 11 as plus-minus, and 12 as positive. Each of these groups will be analyzed separately.

Almost all of the negative Takata-Ara reactions were carried out on different patients. There were a few individuals, however, in which the test was repeated at a later date. It will be recalled that the reaction is designated as negative whenever no two adjacent tubes show at least a "3" degree of precipitate. In the vast majority of these reactions only a trace of sediment was present.

Study of the case records of the patients on whom the 277 negative reactions were obtained reveals that in 11 a clinical diagnosis of cirrhosis was made. Only 2 of these, however, were positively

confirmed by histologic examination of the liver. In 1 of these a biopsy showed a very early periportal cirrhosis, while the other case was autopsied and a typical atrophic cirrhosis was found. However, on 2 other occasions this patient gave strongly positive reactions. In this connection it is interesting to note that in another case which was undoubtedly cirrhosis but was not autopsied, both positive and negative reactions were obtained at different times. A reasonable doubt may be cast on the clinical diagnosis of cirrhosis in 5 of the remaining cases. This leaves 4 of the 11 with negative reactions in which the diagnosis seems quite certain and positive results were never obtained.

It is apparent, therefore, from the findings in this group that cases of cirrhosis do occur with negative Takata-Ara tests. In some of these the negative reaction is transient, and this interval may be preceded and followed by periods during which it is positive.

Plus-minus reactions were obtained in 11 cases. Three of these were clinically quite typical Laennec's cirrhosis and 1 of the 3 was proven later by autopsy. Four of the 11 occurred in individuals having cholangitis with a variable amount of biliary cirrhosis; 1 of these was due to malignancy and 2 to cholelithiasis. Of the 4 remaining cases, 1 was an arsenical hepatitis and another a lymphosarcomatosis with extensive spread in the liver. This leaves only 2 of the 11 cases in which there was no particular involvement of the liver. One was an advanced pulmonary tuberculosis with marked destruction of the adrenals and the other a multiple myeloma.

From these findings it would appear that plus-minus reactions may be considered strongly suggestive of some form of hepatic disease and more particularly a peri-insular or biliary form of cirrhosis.

Reactions were designated positive in 12 cases. Of these, 9 were proven subsequently to be peri-insular cirrhosis by postmortem examination and 2 more were quite typical of this disease clinically. The remaining case of the 12 had a marked obstructive jaundice which was believed due to malignancy. He left the hospital without operation so this diagnosis has never been confirmed pathologically.

From this group one may conclude that Takata-Ara reactions with sufficient precipitate to be classified as positive according to the criteria outlined above occur almost exclusively in cases of peri-insular cirrhosis.

Conclusions. Analysis of a series of 300 Takata-Ara reactions, carried out for the most part on patients who showed a hyperbilirubinemia or gave reason to suspect the presence of hepatic disease, indicates that the test has considerable diagnostic value. It would appear that the difference of opinion which has arisen in the literature concerning its value is due to the use of various techniques and a lack of precision in reading the results. A means is described whereby more accurate results may be obtained.

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ACTIVATED STEROLS AND CALCIUM SALTS IN TREATMENT OF PARATHYROID TETANY.

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McLean has pointed out[2] that there is much evidence to suggest the essentially equivalent therapeutic values of dihydrotachysterol and vitamin D preparations for oral treatment of hypoparathyroidism. This conclusion is based on the lack of any decisive evidence to the contrary, on clinical reports which indicate satisfactory comparisons, and on toxicity experiments with small laboratory animals. The data from this latter type of trials are presented as follows: The "borderline toxic doses" of pure calciferol (crystalline vitamin D_2) are from 5 to 12.5 times as great as for crystalline dihydrotachysterol. Using the figure 5 as representing maximum toxicity, which McLean believes is parallel to potency in maintaining serum calcium level, pure calciferol would be not over one-fifth as potent as the dihydrotachysterol. By definition, 1 mg. of calciferol, or vitamin D_2 is equivalent to 40,000 international or U.S.P. units. The commercial form of dihydrotachysterol, now marketed as "Hytakerol," is a 0.2% solution of pure activated sterol, or 0.5% of the basic sterols, only 40% of which are significantly active. With the above equivalents in mind 1 mg. of calciferol, or 40,000 international units, of vitamin should be as active as 0.2 mg. of dihydrotachysterol, which is contained in 0.1 ml. of the commercial oily solution. Or, in other words, 1 ml. of the oil solution, containing 2 mg. pure dihydrotachysterol (or 5 mg. basic sterols) would be equivalent to 400,000 international units of vitamin. McLean points out that the use of a small unit for the vitamin standardization has tended to discourage the use of large enough doses to demonstrate this usefulness in treating tetany. Doses of Hytakerol commonly in use vary from 0.25 to 2 ml. daily, corresponding to 100,000 to 800,000 units of vitamin D.

An opportunity to test this suggestion was based upon the treatment of 4 cases of tetany which had been under observation for some time previous to the trials to be described. In each of these

patients the beneficial results of appropriate doses of the vitamin as well as of the special preparation have been demonstrated. The choice of therapeutic agent is therefore made a matter of cost and availability of medicament.

CASE 1.—V. T. R. (No. 209579) was first seen at age 27 because of marked thyrotoxicosis, for which a two-stage thyroidectomy was performed, with excellent general results. Although no clinical notes of tetany were found in the convalescent record, and the serum calcium was known to be 9 mg. per 100 cc. on the fifth postoperative day, the patient later mentioned that paresthesias appeared at about the time of discharge from the hospital. She was readmitted 4 months later with the typical symptoms of tetany, including laryngeal stridor and carpal spasm which required use of intravenous calcium gluconate for relief. The following morning serum calcium was 8, phosphorus 6, whole blood cholesterol 129 mg. per 100 cc. The basal metabolic rate was +4%.

Treatment was based on use of a low phosphorus diet, which was continued throughout the observations. Calcium chloride was given in 25% solution, 8 gm. daily. With Hytakerol, given in doses of 0.5 ml. daily, serum calcium was maintained at 10.1 to 10.6 mg., phosphorus dropping to 3.7 and later 2.7 mg. during the first 3 months. The dose of sterol was reduced to 0.25 ml. daily with equally good control, but 0.125 or 0.2 ml. per day led to a drop in calcium to 8.8 mg. and return of tetanic symptoms in mild form.

Transfer was undertaken to vitamin D, using "Ertron," a Whittier process concentrate with 50,000 units per capsule. Dosage of 100,000 units daily for 2 months was not entirely adequate, but 125,000 units was successful, and serum calcium was 9.9 mg., phosphorus 3.7 mg. after 1 week at the higher dose, which eliminated all symptoms of tetany. Return to use of Hytakerol, 0.5 ml. alternate days (0.25 ml. daily), was symptomatically as good, with calcium 9.7 mg., phosphorus 2.5 mg.

These results indicate that 0.25 ml. Hytakerol and 125,000 international units of Ertron are nearly equally potent. It is of importance to the patient, at least, that the former costs just 33% as much as the latter preparation.

CASE 2.—H. P. (No. 221007) was first seen at age 58, some months after thyroidectomy had been done elsewhere, and at which time she showed congestive heart failure and tetany. Serum calcium was 4.5 mg., phosphorus, 2.5 mg. per 100 ml. Treatment with low phosphorus diet and calcium chloride, 4 gm. daily, was insufficient and she was given "Drisdol," a propylene glycol solution of vitamin D. Dosage was uncertain and irregular as an ambulatory patient, and she was hospitalized a second time after a month's interval. With Drisdol doses of 100,000 units daily for 2 weeks, calcium rose from 7.9 to 10.1 mg., phosphorus rising from 2.9 to 3.2 mg. Then the dose was reduced to 50,000 units daily, with calcium dropping to 8.6 mg. and rising to 9, 9.9 and 10.2 mg. in the course of 3 weeks. She was then transferred to use of Hytakerol, 0.25 ml. daily, and after 2 weeks calcium had dropped from 10.2 to 9.2 mg. but phosphorus remained at 3.1 mg. Tetanic symptoms remained in abeyance throughout the period of treatment with vitamin or dihydrotachysterol.

These results suggest that 0.25 ml. Hytakerol is not quite as adequate a dose as 50,000 units of Drisdol. This is a more favorable comparison for the vitamin than the first case, but it is again

significant that the vitamin cost to the patient would have been exactly 3.5 times as great, although both preparations are produced by the same firm.

CASE 3.—D. E. (No. 96338) was first seen at age 21 because of lesions of the nails, skin on hands and feet, and on the tongue associated with allergic sensitivity to monilia. Other findings included numerous minute cataracts in both lenses, positive Chvostek and Trousseau signs, Roentgen ray evidence of markedly increased density of all bones, calcification in brain substance, and serum calcium 8, phosphorus 6.4 mg. per 100 ml. The history indicated that idiopathic tetany had been recognizable since age 5. The treatment of tetany began with the diagnosis at age 21, and was based on low phosphorus diet, a daily intake of added calcium salts, and minimal doses of dihydrotachysterol to abolish all symptoms of tetany. Following each of the trials of lower dosage it has been found necessary to return to 1 ml. daily of Hytakerol. A dose of 0.75 ml. has allowed the recurrence of tetany, whereas doses of 1.5 to 2 ml. cause the serum calcium to rise to 11 to 11.8 mg. Use of the 1 ml. doses daily maintains the calcium at 8 to 9.3 mg., phosphorus 3.3 to 6.1 mg., usually in the lower range, and with entire freedom from tetanic symptoms or signs. After 3 years of such treatment an attempt was made to substitute vitamin D preparations for the dihydrotachysterol. The patient had been economizing by use of 0.75 ml. of the latter preparation for some time, was usually free from symptoms, and had calcium 9.2, phosphorus 5.3 mg. per 100 ml. at the time of change. She was given Mead's viosterol in oil, 10,000 international units per gm., the daily dose being 100,000 units. This was continued for 3 weeks, during which calcium varied from 8.7 to 9.35 mg., and phosphorus was 4.8 mg. No tetanic symptoms occurred. The return to Hytakerol, 1 ml. daily, maintained the calcium at 8.3 to 9.3 mg. but induced a progressive drop in phosphorus to 3.3 mg.

Such findings suggest the essential equivalence of 100,000 international units of viosterol with 0.75 ml. of Hytakerol. At current retail prices the vitamin preparation costs twice as much as the Hytakerol, which led the patient to return to the latter for maintenance.

CASE 4.—C. I. (No. 10759) was first seen at age 53, when she developed acute tetany after thyroidectomy for thyrotoxicosis. Subsequent studies have proved that the tetany is of permanent type. Over a period of 5 years she has had treatment of variable effectiveness, with dietary cooperation far from uniform. During the first year small doses of viosterol, not over 30,000 units, were employed, and supplemented with parathyroid extract. Dihydrotachysterol was first used after more than 2 years with tetanic symptoms. Persistent tendency to frequent, loose stools made control of tetany doubly difficult and seldom responded to any treatment other than use of teaspoonful doses of camphorated tincture of opium after each bowel evacuation. Almost 5 years after the onset of tetany a comparison was made between two vitamin D preparations and dihydrotachysterol. Keeping the patient on low phosphorus and low residue diet, with 3 gm. of calcium chloride added daily ½ hour before meals, she was given 100,000 international units of "Drisdol," the solution of D in propylene glycol. After 10 days the dose was increased to 200,000 units daily. One week later still the vitamin was supplied by "Deltalin," a Lilly capsule containing 50,000 international units each, administering 200,000 units daily. During this entire period of 3½ weeks serum calcium had changed

from 5.8 to 7.6 mg., phosphorus from 5.5 to 5.8 mg., and tetanic symptoms and signs were usually in evidence. Treatment was then shifted to Hytakerol, with doses of 0.5 ml. for 1 week, 0.75 ml. for 10 days, and, finally, 1 ml. daily. With the use of the larger dose serum calcium rose to 8.8 and 9 mg., phosphorus decreased to 4.4 to 5.5 mg. and tetany was completely relieved.

The results obtained with this patient do not give exact equivalent doses, but indicate that 200,000 units of the vitamin D preparations were perhaps as potent as 0.75 ml. of Hytakerol, certainly not as helpful as 1 ml. Comparing the costs at retail, the dihydrotachysterol would cost one-sixth less than the Deltalin, which had only a brief trial, but Drisdol would cost 4.6 times as much as the Hytakerol, produced by the same laboratory.

Results. The results obtained in studies on these 4 patients are tabulated in Table 1. The result quoted from McLean[2] is based on his calculation of the maximum potency to be expected from calciferol. The results herein reported suggest that McLean was conservative in his conclusions, and that commercial vitamin D preparations may be more potent than he stated. The limiting factor in turning to the vitamin preparations is neither ineffectiveness nor "toxicity" of any dangerous sort, but a matter of greater cost than the single product containing dihydrotachysterol, Hytakerol.

TABLE 1.—COMPARISON OF ANTITETANIC POTENCIES OF DIHYDROTACHYSTEROL AND VITAMIN D.

Source of comparison.	Dihydrotachysterol, ml. of 0.2% sol.	Vitamin D		
		Preparation.	Dose, I. U.	Equivalent for 1 ml. Hytakerol.
F. C. McLean[2]	1.00	Calciferol	..	400,000
Patient V. T. R.	0.25	Ertron	125,000	500,000
Patient H. P.	0.25	Drisdol	50,000	200,000
Patient D. E.	0.75	Viosterol	100,000	133,000
Patient C. I.	0.75	Drisdol	200,000	266,000

The relatively high cost of commercial preparations of viosterol in the United States is due in large part to the fact that no preparations containing more than 10,000 international units per gm. have been permitted in commerce with the approval of the Council on Pharmacy and Chemistry of the American Medical Association or under licenses granted by the Wisconsin Alumni Research Foundation. Preliminary steps are known to be under way which will make available the higher concentrations of viosterol for prescription use only and which, it is hoped, will receive the approval of the agencies such as those mentioned. These procedures will drastically reduce the retail prices of the high potency viosterol materials so that the price comparisons mentioned must be understood as of 1941 retail costs.

Another detail in the management of the patient with chronic tetany is the choice of calcium salt for use in addition to the small calcium content of the low phosphorus diets. Calcium lactate has

been used most widely. Calcium gluconate was advocated because of its solubility, ease of absorption, and slightly sweet taste. Calcium phosphate is often prescribed, although the rationale of adding phosphate is incorrect, and in spite of the known fact that phosphates in the intestinal tract will reduce the absorption of calcium when the reaction is not acid. The optimum calcium salt is calcium chloride, because this salt is very soluble in water, tends to produce a slightly acid reaction favoring absorption, and because it furnishes the largest proportion of calcium per gm. of salt. From the molecular weights it can be seen that 1 gm. of the salts will produce the following amounts of the element calcium: gluconate, 93 mg.; lactate, 185 mg.; chloride, 360 mg. In other words, the chloride is 4 times as effective as the gluconate, twice as effective as the lactate when serving as a source of calcium. The chief drawback to its use in oral preparations has been its highly astringent effect in the mouth and pharynx. This can be masked satisfactorily by prescribing the chloride as a 25% solution in a vehicle such as the standard elixir or syrup of glycyrrhiza. Patients have been kept on this very inexpensive preparation with complete satisfaction, using doses of 2 to 4 drams daily well before meals.

Criticism of the chloride has been made on the ground that use of this salt will add an anion to the urine, and this will tend to increase the loss of cations, possibly thereby increasing calcium loss. To test this possibility trials were made with patient D. E. described above. The data are given in Table 2. The intake of calcium in food and drinking water was essentially constant, providing 0.124

Table 2.—Effect of Anions on Calcium Salt Therapy.

3-day period.	Salt used.	Daily dose, gm.	Calcium content, mg.	Urine excretion for 3 days. Volume, ml.	Calcium, mg.
3/25–27 . .	Gluconate	4.0	372	2580	234
3/28–30 . .	Gluconate	4.0	372	1560	223
3/31–4/2 . .	Chloride	4.0	1440	1830	137
4/3–5 . . .	Lactate	2.0	370	2290	203

to 0.133 gm. of calcium daily. The use of dihydrotachysterol was discontinued the day before beginning the test, and the patient remained free from tetanic symptoms throughout the 12 days of the study. Serum calcium decreased from 9.2 to 8.7 mg. in this interval. It should be observed that although the chloride provided 4 times as much calcium as the lactate or the gluconate used, and although the extra chlorine to be excreted should increase calcium loss, nevertheless, the urinary calcium was distinctly lower during the period of 3 days' use of chloride than before or after. In spite of the lack of data from fecal analysis to complete information about a calcium balance it is well known that calcium chloride is well absorbed. The maintenance of several patients with this salt for long periods accords with this fact.

The disadvantage of excessive amounts of inorganic phosphate in the intestine when calcium absorption is being facilitated has been stressed by Ellsworth.[1] Attempts have been made to use a proprietary preparation of calcium phosphate, with effervescent salts, in 2 of the patients described in this report, but with failure to control tetany readily in spite of extremely large doses, and with some tendency to increase in serum phosphate. Experience with another patient who has post-thyroidectomy permanent tetany and who requires 0.25 to 0.4 ml. of Hytakerol daily with 4 gm. of calcium chloride, indicates that milk is to be excluded from the diet. When using milk daily the serum phosphate averaged 5.15 mg. for 6 months but when the milk was omitted the phosphate dropped to 4 to 5.1, average 4.7 mg. for 10 months. During these two periods, calcium remained at the same average level of 8.9 and 8.8 mg. but varied from 6.8 to 10.4 mg. while using milk, only from 7.7 to 9.9 mg. when milk was excluded.

Summary. Comparisons in 4 patients with tetany indicate that large doses of vitamin D may serve to control serum calcium and phosphorus levels adequately, but that at current prices this entails an increase in cost to the patient of 2 to 6 times that required for similar success with use of dihydrotachysterol.

Use of calcium as the chloride is advocated, and its superior efficiency in furnishing calcium is combined with safety and palatability when the salt is dispensed as a 25% solution in the syrup or elixir of glycyrrhiza.

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USE OF SULFATHIAZOLE IN INFECTIOUS MONONUCLEOSIS.

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During the past 5 years we have observed 64 university students suffering with infectious mononucleosis. Of these, 29 gave positive heterophil-antibody tests. Of the remaining 35, the test was negative in 7 and was not done in the others. This paper is concerned with only the 29 serologically positive cases, 7 of which were treated with sulfathiazole.

It has been our observation that patients with this disease experience rather protracted periods of disability following the subsidence of the acute phase of the illness. The usual procedures employed in management and therapy have proved uniformly disappointing. In view of the infectious nature of the disease, as characterized by onset with sore throat, fever, lymphadenopathy and occasional rash, it was thought that sulfathiazole might be expected to control more effectively the course and duration of the infectious process. We have therefore employed the drug in the treatment of our more recent cases in accordance with the following general plan. An initial dose of 1 gm. of sulfathiazole was given, followed by 0.5 gm. every 4 hours for the first 2 days. Dosage was then reduced to 0.5 gm., 4 times daily, this amount being continued usually for a period of 4 to 8 days. Seven cases received this form of chemotherapy (Table 1, Cases 14, 23, 24, 25, 26, 27 and 29). In the sulfathiazole-treated cases complete blood counts and urinalyses were performed daily and the urinary output was kept above 1200 cc. per 24 hours. Careful hematologic studies are mandatory when using a drug which is capable of producing a leukopenia in a patient in whom the neutrophils are already frequently reduced.

The limited number of patients treated does not warrant a definite appraisal of the value of sulfathiazole in the treatment of infectious mononucleosis. However, the results obtained indicate that it is definitely superior to any form of therapy previously employed in this disease. Clinically, all patients receiving the drug showed definite and prompt improvement. Fever, sore throat, malaise and much of the adenopathy had disappeared after 4 or 5 days. In those patients who did not receive sulfathiazole, the above symptoms persisted for varying periods up to 2 to 4 months, as usually occurs in this disease. Sulfathiazole did not produce any appreciable change in the blood picture in any of the patients in this series. Our previous experience with sulfanilamide in infectious mononucleosis had been disappointing.

Guthrie and Pessel[5] noted that a transient neutrophilia might appear at the onset of infectious mononucleosis in young adults, with subsequent lymphocytosis which sometimes does not appear until the temperature has returned to normal. Bernstein[1a] found an increased percentage of neutrophils with a normal total white blood count at the onset in only 1 patient. He believes that blood counts are usually not made until 4 or 5 days after the onset of symptoms and by that time a well-marked lymphocytosis is generally present. In none of our patients did we observe a marked neutrophilia at any time during the course of the disease. However, a normal total white blood count and a normal differential picture was present early in the disease in several patients (Table 1).

The initial white blood count, the count taken on the first day of observation of the patient, was 8000 or less in 44.8% (13) of our

cases (Table 1); in 20.7% (6) it was above 15,000. These counts were all taken within 14 days after the onset of symptoms.

The initial differential picture was essentially normal in 20.7% (6). In 72.4% (21) the percentage of lymphocytes was definitely increased (above 40%) on the initial count and in 55.2% (16) the percentage of neutrophils was decreased (less than 40%).

The highest white blood count encountered in this series was 26,400 (Case 28, Table 1). Much higher counts have been observed; 60,000 (Potter[7]) and 54,500 to 63,000 (Tidy[8]). The lowest count in our series was 3700 (Case 24, Table 1). Bernstein[16] noted white blood counts below 4000 in 7 cases. Others have reported counts as low as 2400 (White[10]), 2150 (Blum[2]), 2000 (Tidy[8]) and 1500 (Davidsohn[3]). The highest count in our series was taken on the second day after onset of symptoms and the lowest was taken on the fourth day.

TABLE 1.—LEUKOCYTE AND DIFFERENTIAL COUNTS.

Case No.	Name.	Sex.	Age.	Initial count						Day of initial count.
				W.B.C.	P.	L.	M.	E.	B.	
1	W. A. B.	M	22	14.7	24	66	10	..	..	11
2	T. N. M.	M	24	11.2	29	66	4	..	1	4
3	K. E. VanB.	M	23	5.6	62	36	2	..	..	6
4	G. H. C.	M	23	10.8	41	56	2	1	..	8
5	J. C. G.	M	21	5.6	43	46	1	10	..	7
6	R. F. H.	M	22	4.1	60	35	4	1	..	3
7	W. O. LaM.	M	23	10.1	24	72	4	..	..	3
8	W. H. S.	M	23	7.5	52	40	7	1	..	6
9	L. L. T.	M	23	15.8	41	58	1	..	..	3
10	E. R. K.	M	24	6.1	45	51	4	..	..	2
11	W. H. W.	M	22	11.0	35	57	4	4	..	11
12	J. W. D.	M	21	6.6	52	41	6	1	..	7
13	P. M. Z.	F	21	13.5	24	74	2	..	..	1
14	S. B.	F	19	13.0	17	74	7	2	..	4
15	J. J. Z.	M	25	22.7	27	69	4	..	..	14
16	L. W., Jr.	M	22	7.9	56	35	7	2	..	4
17	E. B. W.	M	27	6.9	38	51	7	3	1	3
18	G. A. R.	M	19	18.0	24	66	10	..	..	4
19	R. L. H.	M	19	6.2	62	29	4	4	1	2
20	C. R. G.	M	20	16.0	32	65	3	..	..	4
21	J. H. F.	M	19	9.0	68	32	..	..	..	1
22	J. R. T.	M	25	6.3	72	25	2	1	..	12
23	R. L. S.	M	22	10.1	27	66	7	..	..	7
24	A. W.	M	25	3.7	67	30	3	..	..	4
25	R. B. C.	M	22	18.1	27	68	5	..	..	4
26	R. J. J.	M	23	7.5	21	71	7	1	..	12
27	C. E. T.	M	22	8.0	23	70	7	..	..	7
28	J. D. L.	M	20	26.4	26	62	9	2	1	2
29	R. C. P.	M	22	12.1	28	64	8	..	..	3

From our observations there was apparent no definite correlation between the total white blood count and the differential picture; between the total white blood count and the stage of the disease; or between the differential picture and the stage of the disease. The only constant finding was a definite lymphocytosis at some time during the course of the disease.

During the first 2 weeks of symptoms the initial white blood count varied considerably in different individuals. We have seen a normal total white blood count with a normal differential picture; a normal total count with a decrease in percentage of neutrophils and an increase in percentage of lymphocytes; and an increased total count with a decrease in percentage of neutrophils and an increase in percentage of lymphocytes (Table 1). In this series a leukocytosis was encountered in only those cases where the lymphocytes exceeded in percentage the neutrophils.

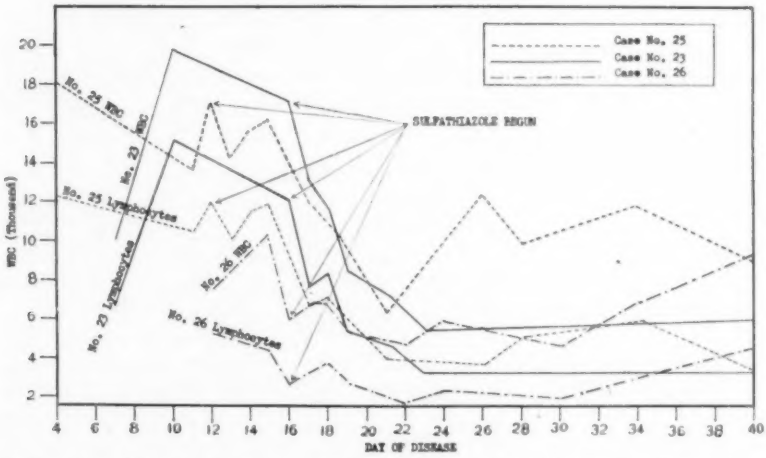

CHART 1.—Total leukocyte counts and number of lymphocytes in three cases treated with sulfathiazole.

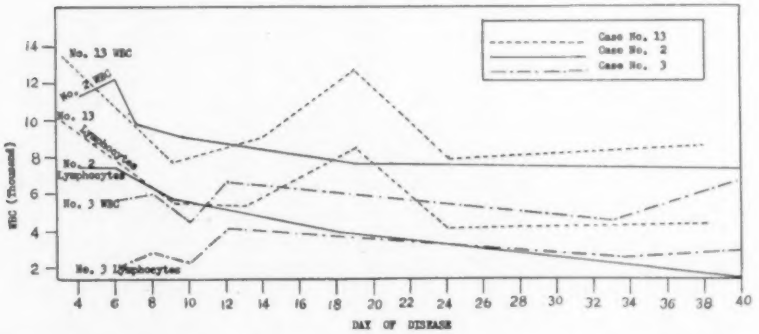

CHART 2.—Total leukocyte counts and number of lymphocytes in three untreated cases.

The symptoms in our 29 cases did not differ from those commonly observed in infectious mononucleosis. The most common and most marked were fever (89.7%), sore throat (72.4%) and general

malaise (72.4%). Less common were headache (41.4%), vague aches and pains (24.1%), tender cervical and axillary nodes (17.2%), chilly sensations and actual chills, nausea and vomiting. Nasal congestion was present in 58.6% (17 cases), acute tonsillitis in 10.3% (3) and Vincent's infection of the gums and pharynx in 6.9% (2). A palpable spleen was present in 31% (9). Cervical lymphadenopathy was noted in 100% (29), axillary in 82.8% (24), and inguinal in 75.9% (22). The usual course of the disease following the acute episode was one of general malaise, ready fatigue, and slight morning or afternoon elevation of temperature for several weeks, persisting in some cases for 4 months or more.

Although the name indicates that the disease is infectious, we have never seen any direct evidence of person to person spread through contact. We have not had more than 1 case from a single fraternity house or dormitory at any one time. Several cases have been present on the campus at the same time, but these usually came from varied student groups having little or no contact with one another. Bernstein[1b] suggests that the "contagiousness" is low and that the occurrence of sudden outbreaks suggests the possibility of the carrier state. West,[9] Guthrie and Pessel[5] and Gooding[4] have reported epidemics of the disease.

The age group of our patients ranged from 19 to 27 years, this being the age group of the university students with which we come in contact.

Of our 29 cases only 2 (6.9%) were females. However, female students comprise approximately only 13.5% of all cases treated at the Student Health Service. Bernstein[1b] noted the disease to be more prevalent in the male sex.

Most of our cases occurred in March and in December, 17.2% (5) in each month; 13.8% (4) were seen in February and in May; and 10.3% (3) in January and in April. Since the University is open for only half of June and September, and for none of July or August, we have no figures for these months. West[9] found no cases in June, July or August, and only 1 in September. He and Bernstein[1b] each found the highest number of cases in their series in October. Gooding[4] reported an epidemic in April and May, and Nolan[6] reported one beginning in November.

In a few of our cases, heterophil-antibody tests done in the first few days of the disease were negative. When the tests were repeated after 1 to 2 weeks, they were found to have become positive. This has suggested the importance of repeating the test during the second week of the disease, as it may not become positive until that time.

Summary. A series of 29 cases of infectious mononucleosis with positive heterophil-antibody tests was studied. Sulfathiazole produced prompt clinical improvement without marked change in the white blood count or differential picture in all 7 of the cases in which it was used.

The heterophil-antibody test was occasionally negative in the first week of the disease and became positive during the second week.

In almost half of the patients the initial blood count was 8000 or less.

ADDENDA. We have seen seven additional patients with infectious mononucleosis since compiling the preceding report. One of these boys, whose initial white blood count was 2000, could not tolerate sulfathiazole because of marked nausea and vomiting. Sulfadiazine was given in one case, but was discontinued because of a resulting high fever and aggravation of symptoms. In five additional cases, sulfathiazole seemed to be of definite value in shortening the symptomatic stage. We have not used convalescent serum in any of these patients.

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AN IMPROVED METHOD OF OBTAINING SUSTAINED CONTROLLED HYPERPYREXIA WITH TRIPLE TYPHOID VACCINE.*

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WHILE treating cases of subacute bacterial endocarditis with a combination of sulfonamides and hyperpyrexia,[1] the conventional method of obtaining temperature elevations with a single intravenous injection of triple typhoid vaccine† was abandoned in favor of a saline suspension of the organism given by continuous infusion. The temperature elevations obtained by this means have been striking. Periods of hyperpyrexia comparable to those obtained with physical methods were obtained with comparative ease and safety. When one considers the relative costs, space and training required for administration of these two methods, the advantages

* This work was aided by a grant from the Joseph Golding Research Fund.

† 1000 million *B. typhosus* per cc.; 750 million *B. paratyph. A* per cc.; 750 million *B. paratyph. B* per cc.

of this simple technique is apparent, warranting further trial and study.

Method. The patient can be treated in his hospital bed; he must be well covered to minimize heat loss. It is advisable to have a nurse in constant attendance. Triple typhoid vaccine in amounts equal to that ordinarily used in the first of a series of typhoid shock therapy injections is added to 1000 cc. of sterilized normal saline. This is thoroughly mixed and added to the sterilized infusion flask which usually has a capacity of 300 cc. This flask is agitated from time to time to insure an even suspension of organisms. The site of preference for insertion of the needle is a forearm vein. It is important to avoid an arm board, as it restricts the patient's activity and makes the treatment harder to bear. An infusion properly applied gives no difficulty even during the most severe chill. The infusion is started at the slowest rate of flow possible (20 to 25 drops per minute). The chill usually occurs within 35 to 45 minutes, and can be suppressed to a considerable extent by injecting into the infusing tubing at the onset of symptoms, morphine sulphate (.015 gm.) and calcium gluconate or chloride (1 gm.). If, as occasionally happens, there is no sign of a chill in 45 minutes, the infusion rate may be doubled. From this point on the temperature may be sustained at the effective level of about 104° F. for as long as 6 to 10 hours without further chills. The maximum temperature elevation usually occurs within 1½ hours after the chill. Rectal temperatures every 10 to 15 minutes are quite important at that time. The infusing rate should not be increased by more than 2 times until the temperature has reached a constant level or has begun to fall. At that time the rate of flow may again be doubled or more feasibly an infusing solution with a greater number of killed organisms may be substituted. As a general rule, the longer the temperature has been elevated the greater the number of organisms or drops per minute required to maintain the temperature at 104° F. If the temperature begins to drop before an effective therapeutic period has been approximated, due possibly to a small number of organisms infused during and immediately after the chill, a considerable quantity of organisms may have to be infused within a short period of time to regain previous temperature levels. Another mild chill is the only possible adverse effect of this rapid infusion.

Elevations or depressions in the temperature can be obtained within 10 to 25 minutes by increasing or decreasing the rate of flow. Excessive rises are controlled by sponging, exposing the limbs or antipyretics. Once the infusion is discontinued, the temperature drops rapidly. Replenishing solutions should usually contain twice the number of organisms as the initial solution. Morphine sulphate (.015 gm.) is given intravenously every 3 to 4 hours for restlessness. In carrying out a series of treatments every day or every other day, the number of organisms used is determined in a manner similar to that of the single injection technique, namely .02 or .03 cc. of triple typhoid vaccine for the first .1, .2, .4 cc. and so on for the succeeding ones.

It is wise to start with a very small number of organisms for the first treatment as there is often a prolonged febrile response and a secondary rise lasting 1 to 2 days. For this reason, we are inclined to feel that since the first injection with its variable response is so often apt to give but a poor temperature elevation, it is simpler to administer only 1 injection of triple typhoid vaccine for the first session. The temperature elevation should be allowed to subside before starting the next treatment. The infusion should not be continued for longer than 6 hours until the febrile responses are properly gauged. As much as 22 cc. of triple typhoid vaccine has been given in an 8-hour session without ill-effects or abnormal tempera-

ture responses. The blood sulfapyridine level is easily fortified by adding 5 gm. of sodium sulfapyridine at the start of the infusion (saline only). All of the patients in this series were receiving either sulfanilamide, sulfapyridine or sulfadiazine (1 gm. every 4 to 6 hours). Supportive therapy is always administered in one form or another.

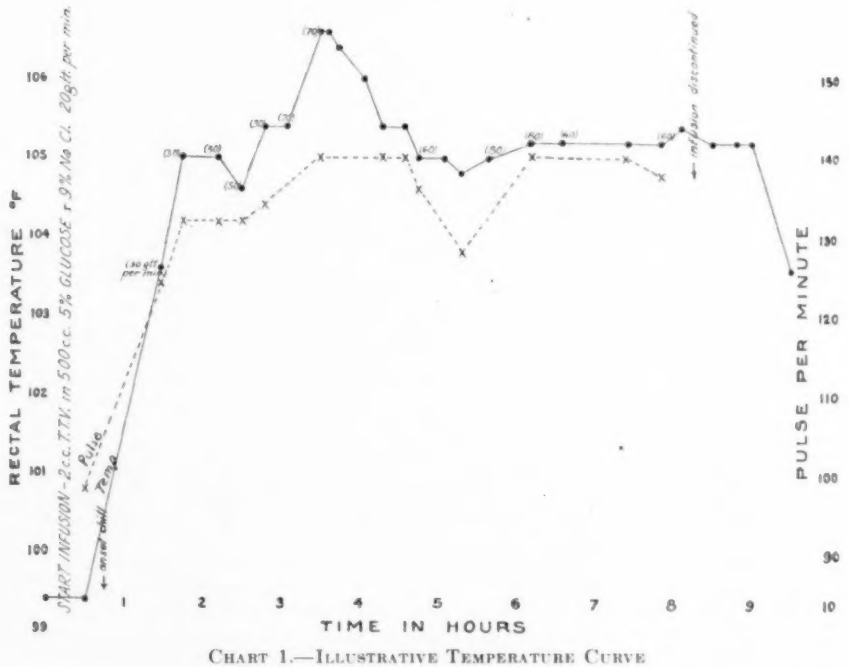

Chart 1.—Illustrative Temperature Curve

Results. Since March, 1941, this method has been used in conjunction with chemotherapy in 14 cases (subacute bacterial endocarditis particularly, and such resistant infections as chronic pyogenic infections of the lung, chronic arthritis, and chronic ulcerative colitis) for a total of 67 treatments. The average length of time the temperature was above 104° F. was 4 hours and 20 minutes.

Two deaths occurred in this series. In 1, a patient who gave evidence of intracranial involvement, diagnosis was rather obscure, possibly that of diffuse vascular disease. The patient had been sick for several months and was deteriorating rapidly. For this reason hyperpyrexia and sulfapyridine therapy seemed to offer the best chance. The cause of death was a sustained and mounting hyperpyrexia with subsequent coma and cardiac failure. The other was a 56-year-old male with multiple aputrid lung abscesses who was markedly toxic and in a critical state. The second treatment using only 100 million organisms caused a prolonged hyperpyrexia which resulted in coma and death.

Several cases of pulmonary suppuration and diffuse fibrosis showed considerable cyanosis, dyspnea and occasional delirium at times. This was rapidly controlled with morphine sulphate (.015 gm.) injected into the infusing tubing. It is important to note that the reactions with this method are quite similar to those of the single injection and usually much less marked.

The therapeutic results with combined therapy will form the subject of another report.

Chart 1 gives a fairly characteristic temperature and pulse curve.

Discussion. The chief drawbacks of hyperpyrexia obtained with a single injection of triple typhoid vaccine are the strenuous chill, the uncertainty of obtaining a suitable temperature rise, the relatively short period of therapeutic fever, the fact that large amounts of the organism must be injected at one time to insure a chill, and the inability to control subsequent course. Attempts have been made to prolong the period of therapeutic fever by giving a doubled dose of triple typhoid vaccine 2 hours after the first.[2] This results in a second chill and all of the unpleasant symptoms of rapid changes in temperature. Here, too, the hyperpyrexia is rarely sustained over 104° F. for longer than 4 hours. One can obtain a well-controlled and sustained hyperpyrexia by using diathermy and hot box. This method is quite costly, requiring special training in its use. Most small hospitals probably do not have this equipment.

Using the infusion technique we have obtained sustained temperature elevations of over 104° F. from 6 to 10 hours with comparative ease. It never presents more of a risk than the single injection technique, for a certain amount of control is always assured. The characteristic result is one chill which can be controlled. The small number of the organisms actually injected to obtain the chill minimizes the dangers of untoward reactions. Adequate amounts of fluid intake are insured by the continuous infusion; and, should collapse threaten, emergency medication can easily be administered through the infusing tubing. A glucose or saline infusion can be readily substituted for the triple typhone vaccine suspension. With but little practice in regulating the intravenous drip, one develops facility in maintaining a fairly level temperature curve. This type of heat seems to be borne comparatively well as compared to diathermy and the hot box, probably because there is less stimulation of the skin temperature endings and less dehydration. The contraindications are those of the single injection: namely, intracranial complications, marked debility and cardiac failure. The presence of endogenous fever does not seem to be a contraindication with this method.

Several interesting sidelights on the physiology of triple typhoid vaccine hyperpyrexia have been noted. The prolonged period of hyperpyrexia which can be varied by changing the rate of infusion of organisms without further chills indicates conclusively that mus-

cular contraction plays no rôle in the maintenance, and possibly none in the production of the fever. The very small number of organisms actually used to bring on the chill is also curious, when one considers how the successive doses of triple typhoid vaccine must be multiplied to obtain adequate temperature elevations. On one occasion 20 cc. of the infusion mixture was injected over 20 minutes after which it was discontinued. This represented a small fraction of the number of organisms one would ordinarily use in one injection to obtain a suitable hyperpyrexia. Much to our surprise, the characteristic chill and temperature elevation resulted. A possible explanation for this may be that the mechanism which removes the organism from the blood stream is far more efficient when a large number is injected at one time than with a slow continuous infusion. The prolonged febrile response resulting from the first injection of typhoid organisms, whether in a single injection or infusion, may be of a similar nature: namely, there is no mechanism to remove the organisms from the blood stream and they continue to circulate and give symptoms for 1 to 2 days until they are removed.

The use of protein shock therapy is a rather old and well-established procedure. Its benefits are probably derived from the hyperpyrexia, increased circulation, stimulation of tissue resistance and antibody formation, and the destruction of lymphocytes with liberation of their antibodies. The recent introduction of chemotherapeutic agents has widened the scope of therapy in general. It is but little appreciated how hyperpyrexia can greatly augment the bacteriocidal properties of the sulfonamides[1,3,4,5] and render effectual a drug which on previous trial had had but little or no effect. This can be carried out with little additional risk to the patient and calls for a reinvestigation of the therapeutic properties of the sulfonamides in other diseases where their use has been discontinued.

Summary. 1. A method for obtaining controlled sustained hyperpyrexia with continuous infusion of triple typhoid vaccine suspensions is described.

2. Using this method in 14 cases for a total of 67 treatments, the temperature was maintained over 104° F. for an average of 4 hours and 20 minutes.

3. It is safe, easy to administer and comparatively economical.

4. The combined use of the sulfonamides and hyperpyrexia offer a therapeutic agent which is far more potent than that of the sulfonamides alone.

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CLINICAL VALUE OF DIGITALIS IN HYPERTENSIVE HEART FAILURE.

I. With a Normal Rate and a Regular Rhythm.

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Digitalis has a substantial background for its use in heart failure with normal rhythm. The first clinician to indicate this was the younger Janeway.[3g] In certain cases with normal rhythm he had seen digitalis followed by as speedy relief of symptoms as in fibrillating hearts; this was particularly true in patients with cardiac insufficiency secondary to prolonged high blood pressure.[6] Pratt[8] found that digitalis is beneficial in some cases of heart failure with normal rhythm. It was Christian[1a,b] who noted that even when the heart rate is slow striking digitalis effects may be produced.

Since then the effects of digitalis on the regularly beating heart have been carefully studied and reported. Luten[7a] stated that the drug exercises an action upon the ventricular muscle which is beneficial independently of any particular cardiac mechanism, and entirely aside from any effect on rate. He added that in administering the drug to patients with normal rhythm it is particularly important to keep clearly in mind the object of therapy, and to appreciate that direct slowing should not be expected; otherwise harmful consequences may ensue. Stewart and his coworkers[9] administered digitalis to decompensated patients with regular rhythm which resulted in 24 hours in an increased cardiac output, a decrease in cardiac size, a shortening of the circulation time, and a fall in venous pressure if it was elevated. Harrison[5] stated that the essential action consists in increasing the efficiency of the heart by diminishing dilatation. Evans[2] emphasized that successful digitalization is best indicated by freedom from symptoms and signs of heart failure, not by actual heart rate. Wood[10] noted that a fall in pulse rate is usually associated with improvement from digitalis therapy, but it is not essential. The drug improves the function of the heart in congestive failure by direct action on the cardiac muscle, which without primary change in the diastolic length of the muscle increases the tension which the muscle can develop in systole.[4] Many leading clinicians, on the basis of their own experience, have long maintained that the true indication for digitalis has little to do with rate or rhythm.[7b]

All of the earlier studies on the use of digitalis in heart failure with normal rhythm have included not only cases due to various etiologic factors, but also those with sinus rhythm and sinus tachy-

cardia. Since the etiologic cause of myocardial failure is regarded as very important today, this study is confined to cases with a single etiologic factor. Further, due to the fact that some still question the effects of digitalis on the heart muscle itself, only cases with a regular rhythm whose rate was between 60 and 99 beats per minute are included. Those cases with a rapid, regular rate of 100 to 160 beats per minute are considered in a separate study.[3b]

In a previous report[3a] on the disturbances of rate and rhythm among 800 cases of uncomplicated hypertensive heart disease, congestive failure with a normal rate and a regular rhythm was noted in 191 patients (23.8%). This was the third largest group among the hypertensive patients; auricular fibrillation, the second largest group, occurred in 198 (24.8%); and the largest were those with sinus tachycardia, which was present in 222 (27.8%). Such a group of patients, representing approximately one-fourth of all cases of hypertensive heart failure, have received little or no attention in the literature. Since it was found that these patients have the lowest mortality of all groups or hypertensives during congestive heart failure, a separate record and analysis was made of all subsequent cases.

Even to one interested in cardiology, patients in congestive failure with normal rate and regular rhythm are the least interesting of all cardiac cases. Such patients have no spectacular symptoms or findings to offer an observer. For this reason it is easy to overlook their failure in the early stages. Aside from the gradual onset with symptoms of dyspnea, and/or precordial or epigastric distress, and palpitation, and the physical findings of an enlarged heart, no other complaints or alterations may be present. Usually, moist râles are present at the bases of the lungs with isolated failure of the left ventricle; while with the combined left- and right-sided failure, in addition to the râles, an enlarged tender liver and edema are found. Seldom does the onset occur abruptly with such alarming symptoms as paroxysmal nocturnal orthopnea, cardiac asthma, or Cheyne-Stokes respiration.

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO AGE.

Age groups.	Male.	Female.	Total.	%.
25–30	1	0	1	0.7
31–40	5	0	5	3.1
41–50	40	12	52	32.5
51–60	65	8	73	45.6
61–69	23	6	29	18.1
Totals	134	26	160	100.0

The material in this study is based on the clinical analysis of 160 cases of hypertensive heart failure who had a normal rate and a regular rhythm at the onset and during the congestive failure. They were seen in succession, and selected only in the sense that each had the heart failure on the basis of essential hypertension; 83%

were males and 17% were females. The ages varied from 25 to 69 years (Table 1); 78.1% were in the hypertensive age of 40 to 60 years. Among all hypertensives 78.8% were in the same age group,[3b] while in 158 with auricular fibrillation 77.1% were in the same ages.[3c]

Duration of Symptoms in Relation to the Outcome. As far as could be personally determined, all of the patients were in their first decompensation. Many of them had been under observation at one time or another for a variety of ailments. About one-third had the psychoneurotic complaints of headache, dizziness, tinnitus, and 23 other similar symptoms.* Regardless of the duration of the symptoms before treatment with digitalis was started, the prognosis was the same (Table 2). The majority, 82 (51%), had the symptoms less than 4 months.

TABLE 2.—DURATION OF CARDIAC SYMPTOMS IN RELATION TO THE MORTALITY.

Duration.	Cases.	Deaths.	Mortality (%).
Less than 1 mo.	39	9	23
1–2 mos.	22	5	22.7
2–4 "	21	6	28
4–6 "	19	5	26
6 mos.–1 yr.	18	5	26
Over 1 yr.	41	7	17
Totals	160	37	23

Type of Heart Failure. There are three types of hypertensive heart failure: 1, the combined right- and left-sided ventricular failure, denoted by symptoms of dyspnea alone or associated with cardiac pain, palpitation, or weakness, with the signs of systemic congestion; 2, isolated failure of the left ventricle, denoted by symptoms of dyspnea or cardiac pain alone or by dyspnea associated cardiac pain, palpitation, or weakness, and no signs of systemic congestion; and 3, isolated failure of the right ventricle, denoted by the symptom of epigastric pain usually, and with signs of systemic congestion.[3d] Among all types of hypertensives the combined type of failure was noted in 72.5% and left ventricular failure in 26.5%.[3d] In the present series of 160 cases the incidence was 66.8% and 33.2%, respectively. The type of hypertensive heart failure has prognostic significance, but in this study the difference in mortality was not as marked. Of those with combined failure, 27 (25%) died, as compared with 10 (18%) of those with isolated failure of the left ventricle (Table 3).

TABLE 3.—TYPES OF HYPERTENSIVE HEART FAILURE IN RELATION TO MORTALITY

Type.	Cases.	Deaths.	Mortality (%).
Combined ventricular	107	27	25
Left ventricular	53	10	18

* Unpublished data.

Duration of Decompensation. The length of time required to restore compensation in these patients seems to have an influence on the outcome. From Table 4 it is noted that the longer the decompensation persisted after treatment with digitalis was begun, the greater the average mortality. Fatalities were heaviest among those whose myocardial failure persisted 6 weeks or longer after treatment commenced.

TABLE 4.—DURATION OF DECOMPENSATION IN RELATION TO MORTALITY.*

Duration.	Cases.	Deaths.	Mortality (%).
Less than 2 wks.	79	12	15
3 wks.	30	6	20
4 "	24	6	25
6 "	13	4	30
8 "	5	3	60
12 "	6	4	66
16 "	3	2	66

* After treatment with digitalis has started.

Causes of Death. Uremia, the important cause of death among these patients, was responsible for 19 (51%) of the 37 deaths during treatment. This is a factor which cannot be controlled by digitalis or by any other type of therapy at the present time. Regardless of the type of failure, it was still the common cause of death (Table 5). Ranking second in importance were congestive heart failure, especially among those with the combined type, and coronary thrombosis, in those with failure of the left ventricle. The frequency and importance of coronary thrombosis occurring during isolated failure of the left ventricle due to essential hypertension has received the special attention it merits.[3e]

TABLE 5.—CAUSES OF DEATH IN 37 CASES OF HYPERTENSIVE HEART FAILURE WITH NORMAL RATE AND REGULAR RHYTHM.

Cause of death.	Combined ventricular failure.		Left ventricular failure.		Total.	%.
	Cases.	%.	Cases.	%.		
Uremia	13	48.0	6	60.0	19	51.0
Congestive heart failure	12	44.4	1	10.0	13	35.0
Coronary thrombosis	1	3.8	3	30.0	4	10.3
Cerebral hemorrhage	1	3.8	..	..	1	2.7

Case Reports. CASE 120. N. C., a 50-year-old male laborer, complained of dyspnea, cough, and palpitation of 3 months' duration. The symptoms had a gradual onset and increased in severity, especially during the last week. He was a known hypertensive, having been originally seen 1 year before at which time a blood pressure of 190/110 and a transverse cardiac measurement of 16 cm. were noted. On this last occasion the physical examination revealed a blood pressure of 210/130, impaired resonance and moist râles over both lung bases, a transverse cardiac measurement of 19 cm., a soft systolic murmur at the apex, and an accentuated second aortic sound. The liver was not palpable and no edema was present. There was a trace of albumin in the urine. The blood urea nitrogen was 38, and the creatinine was 2. He was already on bed-rest, and digitalis, along with sedatives, were given. Three days after treatment was begun

he appeared very drowsy and incoherent. The blood chemistry showed a rise in the urea nitrogen to 62.1 and the creatinine to 6. Although he was digitalized and the failure of the left ventricular cleared, the uremic manifestations increased. Eleven days after treatment was started the urea nitrogen was 120 and the creatinine 9. He expired in terminal uremia 18 days after first being seen for the failure of the left ventricle. An autopsy revealed an eccentric hypertrophy of the heart (620 gm.), arteriosclerotic contracted kidneys with granulation, passive congestion of the liver and lungs, and atherosclerosis of the aorta.

This case is illustrative of the outstanding uncontrollable factor in the course of hypertensive heart failure with a normal rate and a regular rhythm. In spite of a good cardiac response to digitalis, the patient died in uremia.

Case 40.—M. W., a 54-year-old male clerk, complained of dyspnea and precordial pain of 6 months' duration. He was known to have high blood pressure over 6 years, and during those years it varied from 160/90 to 170/110 and the transverse cardiac measurement increased from 14 to 18 cm. On this last occasion the physical examination revealed a blood pressure of 150/96, moist râles at the bases of both lungs, and a transverse cardiac measurement of 22 cm. The liver was not palpable and no edema was present. The urine contained a trace of albumin, and the blood urea nitrogen was 17. An electrocardiogram showed a rate of 86, notching and slurring of the QRS complexes, and negative T waves in Leads 2 and 3. He seemed to respond well to digitalis as the dyspnea and pain diminished and the râles cleared. On the third day after treatment was started he suffered a severe attack of acute coronary artery thrombosis while still in bed. He lingered for 9 days, and expired 12 days after treatment was commenced. An autopsy revealed severe sclerosis of the coronary artery with marked narrowing of the lumen, a recent thrombus occluding the left descending branch of the coronary artery at the site of an atheromatous ulcer, scarring and recent myomalacia in the anterior wall of the left ventricle, marked eccentric hypertrophy of the heart (880 gm.), edema of the lungs, atherosclerosis of the aorta and splenic arteries, chronic passive congestion of the liver, spleen, kidneys, arterio- and arteriolosclerosis of the kidneys.

This case illustrates another uncontrollable outcome in the course of hypertensive heart failure. In spite of what appeared to be a good response to digitalis, death was due to an acute coronary artery thrombosis which occurred on the third day after treatment was started.

Case 64.—H. W., a 54-year-old salesman, was a known hypertensive of 5 years' duration. His blood pressure had varied from 200/120 to 280/150 and the transverse cardiac measurement was 15 cm. On this last occasion, when he complained of dyspnea and nocturia of 6 weeks' duration, the physical examination revealed a blood pressure of 290/150, moist râles at the bases of both lungs, a transverse cardiac measurement of 19 cm., and a booming aortic second sound. The liver was not palpable, and no edema was present. There was a moderate amount of albumin in the urine, and the blood urea nitrogen was 17. Digitalis therapy was instituted. In the midst of what appeared to be a favorable response, he suddenly and very unexpectedly expired while sitting up in bed. His death occurred on the fourth day after treatment was begun. An autopsy revealed marked eccentric hypertrophy of the heart (570 gm.), moderate sclerosis of the coronary arteries, arteriosclerosis of the kidneys, edema of the lungs, and chronic passive congestion of the liver and spleen.

This case might be taken as a failure of response to digitalis, but aside from the evidence of congestive heart failure at autopsy no other factor could account for the sudden death on the fourth day of treatment. Among the 160 cases in this series there was one other sudden cardiac death. This

was in a 50-year-old male, decompensated 2 months, who suddenly expired on the eighth day of treatment when the gross signs of congestive heart failure had already disappeared. An autopsy was not obtainable, and the cause of death, although assumed to be congestive heart failure, was not clear.

Comment. In spite of these unavoidable deaths, a small number of patients with hypertensive heart disease lived 10 to 20 years after the onset of cardiac symptoms.[3f] Considering the large groups of hypertensive patients, those with a normal rate and a regular rhythm have a good prognosis. And those with failure of the left ventricle have a better outlook than those with the combined type of failure.

What the relationship is between the normal rate and the high incidence of uremic deaths, if any does exist, is a question which remains to be explained. It is entirely possible that passive congestion and edema of the kidneys alone are sufficient to interfere with the extraction and filtration of the end-products of nitrogen metabolism. However, it is the force and not the frequency of the heart stroke, working on the principle of a pump, that maintains an adequate circulation. When the force of each beat fails to convey the blood properly, the beats usually increase and a tachycardia further goads the already laboring heart on to failure. In these cases with a normal rate, only the force of the stroke is decreased and for some unexplainable reason an increase in rate does not occur. As long as the rate is normal the blood supply to the heart muscle itself remains adequate. In all other cases of hypertensive heart failure, especially those with sinus tachycardia or auricular fibrillation, the main cause of death is congestive heart failure. Although it may not explain why the rate remains normal, it is possible to assume the following: when the rate is normal, there is no interference with the blood supply to the heart itself; therefore, the heart muscle does not develop any anoxic areas which lead to a more rapid rate, regular or irregular, in the struggle to bring more blood, and with it more oxygen, to the suffocating hypertrophied heart muscle.

Finally, the question is often raised as to whether digitalis is really needed to reëstablish compensation in heart failure with normal rhythm. Such an interrogation may be answered simply. A few decompensated patients with normal rhythm recover without any digitalis, and a few die in spite of adequate digitalis therapy, but in the main the drug reëstablishes compensation and returns to usefulness at least 77% of the hypertensive heart failures with a normal rate and a regular rhythm.

Summary. 1. The study of 160 cases of hypertensive heart failure with a normal rate and a regular rhythm is reported.

2. The age of the patient and the duration of the symptoms before treatment with digitalis apparently had no influence on the outcome.

3. Of all the hypertensive patients who develop congestive heart failure, those with isolated failure of the left ventricle, a normal heart rate, and a regular rhythm have the best prognosis.

4. Factors over which digitalis itself had no control, such as uremia, coronary thrombosis, and cerebral hemorrhage, caused 22 (64%) of the 37 deaths in this series of 160 cases.

5. Treatment with digitalis may be regarded as most successful in these decompensated hypertensive patients, despite the normal rate and the regular rhythm.

The digitalis preparations used in this study were generously supplied by Parke, Davis & Co., and Ciba Pharmaceutical Products, Inc.

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CLINICAL VALUE OF DIGITALIS IN HYPERTENSIVE HEART FAILURE.

II. With Sinus Tachycardia.

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Among hypertensive patients who develop heart failure, the largest group is composed of those who have a rapid, regular cardiac rate of 100 to 160 beats per minute.[2a] Such cases constitute approximately 28% of all hypertensive heart failures, followed by auricular fibrillation in 25%, and a normal sinus rhythm in 24%. The mortality among these hypertensives with sinus tachycardia was 39.2%.[2a] Except for those with A–V nodal rhythm,[2b] which has a mortality of 50%, the hypertensives with a rapid, regular rhythm have the highest fatality rate. It was 20% higher than the mor-

tality among the hypertensive heart failures with a normal, regular rate of 60 to 99 beats per minute.

The symptoms of the majority of these patients have an alarming onset. Usually, an upper respiratory infection, followed by a cough of a week to 10 days' duration, precipitated the acute onset of dyspnea and precordial distress. It was not unusual to have such a hypertensive patient walk slowly into the office, considerably unnerved because of the rapid onset of dyspnea within a short period of time. In addition to the dyspnea and precordial or epigastric distress, many complained also of palpitation and weakness. Frequently the onset came abruptly at night, or following a heavy evening meal, and was characterized by an attack of paroxysmal nocturnal dyspnea, or cardiac asthma, or Cheyne-Stokes respiration.

Physical examination in these hypertensives revealed an enlarged, rapidly beating heart, a rapid regular pulse, and fluid in the lungs, ranging from crepitant râles in one or both bases to acute pulmonary edema, depending on the rapidity and severity of the myocardial failure. This abruptness of failure of the left ventricle appeared extremely serious. If the right side of the heart failed, and it followed shortly after the failure or occurred at the same time in 72.5% of the patients, then an enlarged liver and edema became apparent. Such an alarming onset was in contrast to that of hypertensive heart failure with a normal rate and a regular rhythm, where the symptoms appeared gradually, and the sudden, severe manifestations of myocardial insufficiency were uncommon.[2c]

Because of the differences not only in the onset but also in the rate, this study is based on the analysis of 160 cases of hypertensive heart failure with rapid, regular rhythm. Of this group, 72% were males and 28% were females. Their ages varied from 31 to 67 years (Table 1), and 77.9% were in the hypertensive age of 40 to 60 years. Among all hypertensive patients 78.8% were in the same age groups;[2d] among those with a normal sinus rhythm, 78.1%;[2c] and in 158 cases with auricular fibrillation, 77.1%.[2e]

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO AGE AND SEX.

Ages.	Male.	Female.	Total.	%.
31–40	16	5	21	14.1
41–50	42	24	66	41.1
51–60	46	13	59	36.8
61–67	11	3	14	8.0
Totals	115	45	160	100.0

Duration of Symptoms in Relation to Outcome. Many had been under observation or treatment because of the essential hypertension or other conditions. However, in regard to the duration of symptoms before treatment was started, the mortality did not vary enough to be of any significance (Table 2).

TABLE 2.—DURATION OF SYMPTOMS IN RELATION TO THE MORTALITY.

Duration.	No. of cases.	Mortality (%).
1 mo. or less	40	27.5
1 to 2 mos.	31	32.0
2 to 4 "	11	27.0
4 to 6 "	18	33.0
6 mos. to 1 yr.	30	40.0
1 to 2 yrs.	13	30.0
2 to 5 yrs.	13	23.0
Over 5 yrs.	4	0.0
Totals	160	30.0

Type of Heart Failure. The type of hypertensive heart failure has been shown to have prognostic value.[2f] In this study, where the combined type of right- and left-sided ventricular failure occurred in 72.5% and isolated failure of the left ventricle in 27.5%, it was very apparent. Table 3 indicates that 44 (37.7%) of the 116 patients with combined failure died, while in the 44 with failure of the left side only 5 (11.3%) expired while under treatment.

TABLE 3.—TYPES OF HEART FAILURE IN RELATION TO THE MORTALITY.

Type.	Incidence (%).	Cases.	Deaths.	Mortality (%).
Combined	72.5	116	44	37.7
Left	27.5	44	5	11.3
Totals	100.0	160	49	30.0

Duration of Decompensation. The length of time required to re-establish compensation in these patients appeared to influence the prognosis. Up to 6 weeks after treatment with digitalis was started, the mortality was about the same (Table 4). After that period, if the decompensation still persisted in spite of adequate treatment, the prognosis became increasingly worse.

TABLE 4.—DURATION OF DECOMPENSATION AFTER BEGINNING DIGITALIS IN RELATION TO THE MORTALITY.

Duration.	No. of cases.	Mortality (%).
2 wks. or less	73	26.0
3 "	23	26.0
4 "	23	26.0
6 "	15	27.0
8 "	12	39.0
12 "	6	50.0
16 "	7	71.0
20 "	1	100.0

Causes of Death. Congestive heart failure was the common cause of death (Table 5). All of the deaths due to this controllable factor occurred in patients who had the combined type of failure on presentation. Many of them had apparently dissipated the major portion of their cardiac reserve before the alarming symptoms came on so

abruptly. Uremia (12%) was second in importance and coronary thrombosis (10%) was third. Singularly, of the patients who had isolated failure of the left ventricle, not only was the mortality much less, but none of the 5 deaths were due to congestive heart failure. Coronary thrombosis, which caused 4 of these 5 deaths, had an incidence of 20% among the 44 cases of failure of the left ventricle. This has been emphasized on several occasions.[2f,g] There were no sudden, unexpected deaths among these 160 cases of hypertensive heart failure with sinus tachycardia.

TABLE 5.—CAUSES OF DEATH IN 49 CASES.

	Type of hypertensive heart failure.				
	Combined.		Left.		Total (%).
Causes.	Cases.	%.	Cases.	%.	
Congestive heart failure	34	77.0	..	..	69.0
Uremia	6	13.0	..	..	12.0
Coronary thrombosis	1	2.5	4	80.0	10.0
Cerebral hemorrhage	2	5.0	..	..	4.5
Miscellaneous	1	2.5	1	20.0	4.5
Totals	44	100.0	5	100.0	100.0

Comment. The relationship of tachycardia to heart failure is difficult to determine. It is not unlikely that in many instances the tachycardia precedes and precipitates the heart failure. This has been shown to occur in auricular fibrillation where the arrhythmia was the first sign, and because of the rapid rate, evidence of myocardial insufficiency appeared in a few days.[2a,e] Luten[5a] stated that the tachycardia which occurs in heart failure is a compensatory mechanism secondary to, and not the cause of, the failure. An opposing view is that the tachycardia often develops in the presence of a hypertrophic heart and usually brings on premature failure.[6] During diastole the left ventricle receives its blood supply, and an increase in heart rate interferes with the oxygenation of the cardiac muscle fibers. The tachycardia not only goads the weak muscle to more frequent contractions but deprives the harassed myocardium of adequate nourishment.

In general, among all cases of this etiology, those with a sinus tachycardia have the worse prognosis, excepting A–V nodal rhythm. The rapid rate, caused by infection or exertion or a combination of both, decreased the cardiac reserve and brought on the heart failure. The hypertensive patient in this group stands a better chance of recovery, for congestive heart failure, the common cause of death, is a controllable factor if treated early and adequately. Yet in spite of the alarming symptoms that many of these patients had at the onset of myocardial failure, they did not seek medical attention any sooner than those who had a normal rate and a gradual onset. Some explained that they had had previous attacks but they got over them until this one came along. Perhaps the con-

timued disregard of such ominous signs of heart failure accounts for the high mortality.

The essential drug used in these cases, digitalis, excercises an action upon the ventricular muscle which is beneficial independently of any particular cardiac mechanism, and altogether aside from any effect on rate.[5b] When the drug is administered to these patients with normal rhythm it is especially important to keep clearly in mind the object of therapy, which is the reëstablishment and maintenance of compensation. Direct slowing of the cardiac rate should not be the goal or harmful consequences may ensue. Successful digitalization is best indicated by freedom from symptoms and signs of heart failure, not by the actual cardiac rate.[3] Although a fall in pulse rate is usually associated with improvement from digitalis therapy, it is not essential.[1] When the cardiac rhythm is regular the fact that the rate is rapid is no proof that the heart can stand more digitalis. In some cases the question whether more or less digitalis is needed is one that can be ascertained only through trial and error, for the main point is whether the clinical condition improves with one type of regimen or another.[4]

Summary. 1. The study of 160 cases of hypertensive heart failure with sinus tachycardia is reported.

2. The cardiac rate is important as a prognostic sign, because the mortality among these patients, with the exception of A–V nodal rhythm, was the highest of all groups of hypertensives.

3. Exempted were those with isolated failure of the left ventricle where the mortality, due chiefly to coronary thrombosis, was only 11.3%, as compared with a mortality of 37.7% among those with the combined type of ventricular failure.

4. Congestive heart failure, the factor controllable by digitalis, was responsible for 34 (69%) of the 49 deaths, but all of these were in patients who had the combined type of failure before the treatment was started.

5. Digitalis was administered to these hypertensive patients with rapid, regular cardiac rhythm not for its action on the rate, but to relieve the symptoms and signs of heart failure, which it did successfully in 70% of the patients.

The digitalis preparations used in this study were generously supplied by the Ciba Pharmaceutical Products, Inc., and Parke, Davis & Co.

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BOOK REVIEWS AND NOTICES

CLINICAL HEMATOLOGY. By MAXWELL M. WINTROBE, M.D., PH.D., Associate in Medicine, Johns Hopkins University; Associate Physician, Johns Hopkins Hospital, and Physician-in-Charge, Clinic for Nutritional, Gastro-Intestinal and Hemopoietic Disorders, Baltimore. Pp. 792; 167 illustrations and 7 colored plates. Philadelphia: Lea & Febiger, 1942. Price, $10.00.

THE author, one of the acknowledged leaders in hematology in this country, offers an accurate, carefully prepared treatise on a subject that has received many important additions in recent years. In achieving his goal of a systematic presentation that sifts the more from the less important, he details the best of the new methods, gives a guide to differential diagnosis and treatment, and yet finds space to clarify the fundamental nature of the disease processes concerned. The information is organized from "thousands of publications," 2400 of which are referred to at the ends of the various chapters.

One naturally finds some items that seem capable of improvement: among them, for instance, the concept of the placental origin of erythroblastosis fetalis should have been given; especially in war time, one would have liked to have found mustard gas included as a cause of leukopenia; Minot's Nobel prize-winning achievement in removing pernicious anemia from among the uniformly fatal diseases is surprisingly underemphasized; Feitis' Fleckmilz might have received brief notice. The author has maintained such marked reserve in the complex field of the lymphomatoid diseases, and so many types are considered, at least in part under common headings, that attainable clearness is not attained.

A novel arrangement of the various sections devoted to each disease reserves "Pathology" (really "Pathologic Anatomy") and "Pathogenesis" as the last items—more suggestive of their position in single case studies than of an orderly consideration of the disease process. Many will find the Appendix on comparative hematologic data and references very useful. The format is excellent. The illustrations, which include camera lucida drawings and photographs of living blood cells, really illustrate, and we have found very few typographical errors.

We believe that the author has well performed the difficult task of making a valuable contribution to a specialty that in recent years has been unusually well supplied with good textbooks. We know of no better book in its field.

E. K.

METHODS OF TREATMENT IN POSTENCEPHALITIC PARKINSONISM. By HENRY D. VON WITZLEBEN, Elgin State Hospital, Elgin, Illinois. Preface by THEODORE J. C. VON STORCH, Associate Professor of Neurology, Albany Medical College; Attending Neurologist, Albany Hospital. Pp. 164. New York; Grune & Stratton, 1942. Price, $2.75.

THIS monograph, on a devastating disease, is by an authority of much experience. In this country, the number suffering from the affection is probably more than 60,000. "Hassler has clearly demonstrated that in most postencephalitic Parkinsonism all groups of cells in the substantia nigra are altered. . . . tremor is due to changes in the anterior part, while

the rigidity is caused by lesions in the posterior part." Three forms of Parkinsonism must be differentiated: postencephalitic, arteriosclerotic, and paralysis agitans.

The author recognizes the following as characteristic of the postencephalitic form: an acute stage of epidemic encephalitis; intensive akinesia and deficiency of mimic and reactive movements; frequent absence of tremor; absence or infrequent appearance of pill rolling; salivation; oily skin; supplementary complications, such as paresis of eye muscles, oculogyric crisis; sleepiness or sleeplessness; more pronounced motor disorders than in paralysis agitans; remarkable improvement with the Bulgarian treatment.

History of the Bulgarian treatment of this disease touches romance. Some 15 years ago, continental Europe was surprised at rumors telling of successes obtained with the secret remedy employed by a layman, named Raeff. Then, through research work inspired by the Queen of Italy, the product and its method of use were revealed.

After considering the other methods of treatment, the writer describes the use of his remedy, "Bulgkaur," which is a standardized total extract from the Bulgarian belladonna root, of proper age and gathered at the proper time. As a rule, treatment is begun with a drop a day, and is increased to from 15 to 25 drops, 3 times a day. Patients showing rigidity usually require larger doses than subjects with tremor. The side effects are similar to those of atropine, but appear later and are milder. An important adjunct to treatment includes physical exercises, massage, calisthenics, the use of splints, and so on. The course is long, difficult, and calls for the utmost patience on the part of both subject and instructor. There are numerous contraindications.

Gratified with the results of his treatment, the author tells of long bedridden subjects displaying marked improvement; and from the social viewpoint of his 837 patients, "71 per cent of all cases succeeded in returning to work." The bibliography covers more than 23 pages. N. Y.

LABORATORY DIAGNOSIS OF PROTOZOAN DISEASES. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel, United States Army Medical Corps, Retired. D.S.M. Emeritus Professor of Tropical Medicine, Medical School, Tulane University, etc. Pp. 349; 54 illustrations, and 4 colored plates. Philadelphia: Lea & Febiger, 1942. Price, $4.50.

THIS book adequately describes all forms of protozoa that are parasites of man, and gives detailed instructions for collecting and examining feces, blood, cerebrospinal fluid and tissues for these organisms. Staining methods, cultivation and animal inoculation also receive careful attention. A considerable bibliography, over 8 pages, is appended. Subjects and authors are indexed separately. The author has given a large part of an active life to the study of parasitic diseases, especially those due to protozoa. No one is better fitted to compile this critical review of the various laboratory methods that have been advocated for the diagnosis of protozoan infections.

H. R.

WILLIAM HENRY WELCH AND THE HEROIC AGE OF AMERICAN MEDICINE. By SIMON FLEXNER and JAMES THOMAS FLEXNER. Pp. 539; illustrated. New York: The Viking Press, 1941. Price, $3.75.

THIS book may be read with equal interest and enjoyment by laymen and doctors. It is the story of a great American and of a great epoch. No man has more profoundly influenced American medicine than Dr. William Henry Welch, the "Popsy Welch" of Hopkins who became a legend while still hale and hearty.

The story tells of Dr. Welch's New England ancestry—a long line of doctors—and of his childhood in the pleasant Connecticut town of Norfolk, which as he wrote many years later "afforded the best this country could offer in the way of heredity and environment for the upbuilding of that strength of character, that soundness of mind and of body, those moral and intellectual ideals which have been in the past (whatever the future may have in store for us) the determining forces in the development and prosperity of our country." When he was sixteen, he went to Yale—a college still walking in its ancient ways, a very different Yale from the great University of today—where he received virtually no instruction in science but where he fell under the spell of the classics; his aspiration at the time of his graduation was to be called back as a tutor of Greek. His conversion to medicine came slowly; after another year at Yale studying chemistry (surely an almost intuitive choice in those days), he left New Haven when 22 years old and entered the College of Physicians and Surgeons in New York. Here he met inspiring teachers; Dr. Welch in later years attributed the "flowering of his interest in medicine not so much to the studies he pursued as to the personality of his teachers." There are many early indications that his interests were directed not toward the practice of medicine but toward a career in the medical sciences. By the time he had reached the age of 25 he was sure that he wanted to become a professor of pathologic anatomy and devote all of his time to teaching and research (such a position, be it remembered, did not then exist in America). Soon afterward he went abroad to study. He was fortunate in the choice of his teachers who, investigators of the first rank themselves, imbued him with the spirit of research. Perhaps he owed most to Julius Cohnheim, for in his laboratory he learned the application of the methods of physiology to the problems of pathology. Now came years of struggle and disappointment in New York, where he established at Bellevue Hospital the first laboratory of pathology. His opportunity came when he was offered a chair in the newly established Johns Hopkins Medical School. Here he became the first member of the faculty of the new school, himself choosing the designation of the chair as "Professorship of Pathology" (instead of, as was then customary, professorship of morbid anatomy, or of pathologic anatomy or of general pathology and like terms). His choice was at the time unprecedented; but it denoted his concept of a pathology which was to cover "the whole broad field of the origin and nature of disease," the science of disease in its entirety. Followed happy years in the laboratory, training assistants, teaching students, doing experimental research. But he also helped in the organization of the school and he assumed the burden of deanship. He founded, and edited for some years, the *Journal of Experimental Medicine*, the first journal in this country devoted purely to the scientific investigation of medical problems. The success of the journal testified at once to the new spirit of inquiry in this country; that the journal survived and today is one of the world's foremost is proof that the awakening was not ephemeral. Of importance equal to the creation of a journal for the dissemination of scientific knowledge was the creation of an institute solely dedicated to the acquisition of knowledge; namely, the founding of The Rockefeller Institute for Medical Research. Dr. Welch's part in the planning of the Institute, and in the fortunate choice of his first Director—the senior author of this biography—was dominant. But all of these activities took him from his laboratory, and his research. Dr. Welch's genius for organization was now so well recognized that he had inevitably become more and more an administrator and public servant, "our greatest statesman in the field of public health," as the President of this country called him on his 80th birthday.

There is much temptation to linger over the writing of this review and speak further of this man who to the generation now ageing was a great symbol. But at best the Reviewer can but spoil the better word picture

which the Flexners, father and son, have given in their book. To those who had not known Dr. Welch in the flesh, there will take form, as the pages are turned, a friendly, tolerant, genial, fun-loving, very human, learned and wise man to whom we all owe much; and those who were so fortunate as to have known Dr. Welch, however, slightly, will love him the more for this story.

B. L.

PSYCHIATRY IN MEDICAL EDUCATION. By FRANKLIN G. EBAUGH, M.D., Professor of Psychiatry, University of Colorado School of Medicine; Director, Colorado Psychopathic Hospital, and Division of Psychiatric Education, National Committee for Mental Hygiene, and CHARLES A. RYMER, M.D., Associate Professor of Psychiatry, University of Colorado School of Medicine; Assistant Director, Colorado Psychopathic Hospital. Pp. 619; illustrated. New York: The Commonwealth Fund, 1942. Price, $3.50.

THERE is discussion in this book that can be valuable to any dean or any teacher who is engaged in fitting a medical curriculum to students' needs. In its examination of the failures and successes of psychiatric teaching it reaches medical education in general.

The material consists of the records of a survey of 68 medical schools in 1932 and questionnaires which have brought these records up to date. The authors have given this material good editing but also have put in their own personal experience, judgment and suggestions so that the book has life.

Premedical college work gets little praise, because of its failure to give the student a conception of a patient who is always affected by the society about him—of a patient who is a person. There is a downright denunciation of courses in abnormal psychology in colleges.

In the medical schools the authors discuss departmentalism, the selection of medical students, teaching techniques, the general situation of the students, the fact that a medical faculty "abhors a vacant hour in the curriculum as nature abhors a vacuum."

Even the chapters on the teaching of psychiatry have a general interest because they give the opinions of surgeons, internists, pediatricians and students about the place of psychiatry and because liaison with other medical teaching is emphasized. The authors see the teaching and clinical facilities of psychiatry as often inadequate, and they divide the blame fairly. There is a full discussion of psychiatry in the general hospital.

E. B.

THE DOCTORS MAYO. By HELEN CLAPESATTLE. Pp. 822; illustrated. Minneapolis: The University of Minnesota Press, 1941. Price, $3.75.

NEVER in the history of this country, perhaps even of the world, have two brothers, starting so modestly, attained such proficiency and prominence in the medical profession and collaborated in using this prominence so constructively in forwarding medical science and practice. The story of such a remarkable achievement is necessarily an enthralling one, and Miss Clapesattle, the historian and editor of the Minnesota Press, has made good use of the free access she has had to a rich source material.

From the time that William Worrall Mayo, "The Old Doctor," left England in 1845, to the death of his more famous sons—within 2 months of each other—in 1939, the family story is unrolled—the father's pharmacist days at Bellevue, his pioneer and Civil War days in Minnesota, his domicile in Rochester, the cyclone of 1883 that brought together the doctor and the sister who started the beginnings of the great Medical Center, international recognition, and the Foundation that ensured continuance of the medical training center for future generations. Each an outstanding surgeon in

his own field, the brothers were among the first to realize the importance of coöperation in medicine and were successful in gathering good men to work with them. It is the brothers who dominate the book, however, and the human touch with them has been preserved with frequent glimpses of personal characteristics and anecdotes.

The illustrations would illustrate better if they were not rather awkwardly gathered into four groups, presumably for binding purposes. The study is unusually well documented with 83 pages of bibliographic notes and is adequately indexed. It has obviously been prepared with great care; and yet, perhaps because of the tremendous prepublication publicity by advertisement, colored postcards and news releases, one lays it down without the feeling of satisfaction that had been anticipated. It is a praiseworthy but not a great biography; and more valuable as an authoritative record than as an entertaining story. But how often should one expect a Cushing's "Osler" in one generation? E. K.

THE BLOOD BANK AND THE TECHNIQUE AND THERAPEUTICS OF TRANSFUSIONS. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital; City Bacteriologist, Atlantic City; Serologist, Municipal Hospital for Contagious Diseases, Atlantic City; etc., and MICHAEL DEBAKEY, B.S., M.D., M.S., F.A.C.S., Assistant Professor of Surgery, School of Medicine, Tulane University of Louisiana; Visiting Surgeon, Charity Hospital, Touro Infirmary, and Mercy Hospital, New Orleans, etc. Pp. 558; 214 illustrations. St. Louis: The C. V. Mosby Company, 1942. Price, $7.50.

THIS book covers the entire field of transfusion, including the most recent innovations, such as the use of plasma and serum. The search of original sources has been most thorough, and the bibliography itself is very valuable. This presentation has avoided the superficialness of some textbooks. The Reviewer commends particularly its wealth of small but essential detail, and its emphasis on the need for a meticulous technique and a conservative attitude, essential for patient safety. The book may be warmly recommended to those concerned with any phase of transfusion from donor selection to the clinical use of whole blood and plasma. W. B.

PHYSICAL MEDICINE. The Employment of Physical Agents for Diagnosis and Therapy. By FRANK H. KRUSEN, M.D., F.A.C.P., Associate Professor of Physical Medicine, The Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, The Mayo Clinic, etc. Pp. 846; 351 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, $10.00.

THIS is a welcomed edition to the textbooks on this important and growing subject. The author has carried out a definite plan which includes the physics, method of production, physiologic effects, technique, indications and contraindications of each subject. This makes a very effective and complete covering of each subject considered and enables the physician to obtain the desired information without having to digest too much extraneous material. Each subject is also covered by a full reference to literature and the opinion of various authorities on the subject. As the opinions are at times directly opposed, there is a tendency for one to become confused if he ventures too far into the résumé of the literature. For those who want to pursue the subject, it constitutes a very valuable source of information.

Artificial Fever is covered in a very complete and concise manner and presents a modern concept of the entire subject of fever therapy in a very practical way. This is one of the best features of the book. Various types of electrotherapy are very clearly discussed and their indications and

technique properly described. Of particular value are the chapters on Diathermy where the author has assumed a very sensible attitude without dogmatic statements. The use of diathermy in diseases of various parts of the body is discussed but unfortunately the directions as to technique is not definite enough to enable the beginner to employ these methods intelligently. The chapters on Hydrotherapy and Mechanotherapy fill a very valuable place as these are subjects which are all too frequently neglected and information on their use is only to be found in specialized textbooks. Inasmuch as they should be associated with the use of Physical Therapy, it is a very valuable thing to have them so well covered by a textbook of this type.

The seventh chapter of the textbook dealing with the clinical aspect of physical medicine discusses its use in the various specialties and is principally a quotation of the opinion of various authors on the use of Physical Therapy in these various specialties. The chapter is very valuable to one who is well versed in physical therapy but for the beginner there is too much of a tendency to confuse the issue as no definite statements are made as to the author's stand on the various subjects.

In general, the book fills a long-felt need and will be of great value to the present practitioner as well as to the beginner in the use of Physical Therapy.

W. S.

From Infancy through Childhood. By Louis W. Sauer, M.D., Ph.D., Assistant Professor of Pediatrics, Northwestern University Medical School, Chicago; Physician, Evanston Hospital, Evanston, etc. Pp. 200; 13 illustrations. New York: Harper & Brothers, 1942. Price, $2.00.

This volume, in size and content, can be classified as a pocket manual or guide book to child-bearing and child-rearing. In a simple and condensed manner it covers, in a practical way, the more common problems presented by the prenatal period, a discussion of breast and bottle feeding, and a résumé of vitamin requirements and balanced diets.

The physical and mental health of the infant and growing child are briefly considered, as well as the more common diseases of childhood.

A chapter is devoted to the special problems of the premature infant, and another to the adopted child. In an appendix is included the more frequent accidents that may befall the child, and a list of poisons and antidotes.

The author does not intend that the book be more than a practical guide to be used in conjunction with, not instead of, direct medical supervision. As such, the volume is well composed, and so written as to be readily comprehended by the average mother.

M. C.

Diabetes Mellitus. By Zolton T. Wirtschafter, M.D. and Morton Korenberg, M.D. Pp. 186. Baltimore: The Williams & Wilkins Company, 1942. Price, $2.50.

This book of 13 concise and clearly written chapters, has been written, according to the authors' preface, for the information of those who wish to understand the abnormal processes which underlie diabetes and what may be accomplished in the way of treatment. It is in no sense a textbook from which details of treatment may be obtained. One of the valuable features of the book is a bibliography of over 300 scientific articles which includes the most important literature of recent years on the subject of diabetes. The book is well indexed so that subjects are easily found. The reading is easy, but one might wish that the authors had treated the chapters on vitamins and endocrines more fully. However, the book is a valuable contribution to the literature on diabetes.

R. R.

NEW BOOKS.

The Structure of Protoplasm—A Monograph of the American Society of Plant Physiologists. By WILLIAM SEIFRIZ. Pp. 283; illustrated. Ames: Iowa State College Press, 1942.

Surgery of the Ambulatory Patient. By L. KRAER FERGUSON, A.B., M.D., F.A.C.S., Lieut.-Commander, Medical Corps, U. S. Naval Reserve; Assistant Professor of Surgery, University of Pennsylvania, etc. With A Section on Fractures by LOUIS KAPLAN, A.B., M.D., F.A.C.S., Associate in Surgery, University of Pennsylvania. Pp. 923; 645 illustrations. Philadelphia: J. B. Lippincott Company, 1942. Price, $10.00.

The Conquest of Bacteria—From Salvarsan to Sulphapyridin. By F. SHERWOOD TAYLOR. Foreword by HENRY E. SIGERIST. Pp. 175. New York: Alliance Book Corporation, 1942. Price, $2.00.

The Clinical Application of the Rorschach Test. By RUTH BOCHNER, M.A., Psychologist; Formerly Bellevue Psychiatric Hospital; and FLORENCE HALPERN, M.A., Psychologist, Bellevue Psychiatric Hospital. Introduction by KARL M. BOWMAN, M.D., Professor of Psychiatry, University of California Medical School, San Francisco, Calif. Pp. 216; 20 records. New York: Grune & Stratton, 1942.

Pediatric Gynecology. By GOODRICH C. SCHAUFFLER, A.B., M.D., Assistant Clinical Professor of Obstetrics and Gynecology, University of Oregon Medical School, etc. Pp. 384; 66 figures. Chicago: The Year Book Publishers, Inc., 1942. Price, $5.00.

Neural Mechanisms in Poliomyelitis. By HOWARD A. HOWE, M.D., Associate in Anatomy, The Johns Hopkins University, Baltimore, Md., and DAVID BODIAN, PH.D., M.D., Assistant Professor of Anatomy, Western Reserve University, Cleveland, Ohio. Pp. 234; 58 illustrations. New York: The Commonwealth Fund, 1942. Price, $3.50.

L'état Pré-cancérous-Signification Biologique. By J. M. MONTPELLIER, Professor of Pathological Anatomy, School of Medicine, University of Algiers, North Africa. Pp. 268; numerous illustrations. Algiers: Jules Carbonel, 1941. Price, about $2.00.

The Schering Clinical Guides. A Three-volume Review of Modern Sex Endocrinology. Vol. 1—Female Follicular Hormone Therapy—58 pages. Vol. 2—Corpus Luteum Hormone Therapy—47 pages. Vol. 3—Male Sex Hormone Therapy—52 pages. Prepared and published by the Schering Medical Research Division, Schering Corporation, Bloomfield, N. J., 1942.

NEW EDITIONS.

The Principles of Neurological Surgery. By LOYAL DAVIS, M.S., M.D., F.A.C.S., PH.D., D.Sc. (HON.), Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago, Ill. Pp. 503; illustrated, with colored plates. Second Edition. Philadelphia: Lea & Febiger, 1942. Price, $7.00.

Symptom Diagnosis. Regional and General. By WALLACE MASON YATER, A.B., M.D., M.S. (IN MED.), F.A.C.P., Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine; Physician-in-Chief, Georgetown University Hospital; Physician-in-Chief, Gallinger Municipal Hospital, Washington, D.C. Pp. 900. Fourth Edition. New York: D. Appleton-Century Company, 1942.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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WHAT THE U. S. PHARMACOPŒIA XII MEANS TO THE PHYSICIAN.

BELIEVING that every physician owes it to himself and to his patients to keep fully informed in the field of therapeutics, the editors are of the opinion that this department can serve its readers best by discussing the forthcoming Pharmacopœia of the United States, U.S.P. XII. Unfortunately, the majority of physicians seem to know little or nothing about this great compendium which makes it possible for them to treat their patients safely and as skilfully as their therapeutic knowledge permits. The United States Pharmacopœial Convention of 1940 adopted 26 general principles to govern the work of revision the first of which is: "The object of the Pharmacopœia is to provide standards for drugs and medicines of therapeutic usefulness or pharmaceutic necessity, sufficiently used in medical practice within the United States or its possessions; to lay down tests for the identity, quality, and purity of these; to insure, so far as practicable, uniformity in physical properties and active constituents. It is recommended that the Committee of Revision be authorized to admit into the Pharmacopœia a carefully selected list of medicinal substances of known origin, but no substance or combination of substances shall be introduced if either the composition or mode of manufacture thereof be kept secret." This defines clearly the purpose of the volume and specifically limits its scope. Congress, by the terms of the Food, Drug and Cosmetic Act establishes each revision as the law of the land with reference to the substances described therein and which thereafter are termed "Official." The U.S.P. thus provides authoritatively a selected list of substances and their preparations which are of definitely established therapeutic value in the light of the best current scientific knowledge. It then seeks to establish all workable means to insure to both physician and patient

that these official agents shall be of uniform purity and standard potency.

The process of revision is a task of far greater magnitude and difficulty than can well be appreciated by anyone who has not participated. It is performed under the direction of the Committee of Revision made up of about 50 recognized experts elected by the Convention from those who are willing and are best qualified to serve. This group represents almost every special field covered by the Pharmacopœia, including Medicine, Pharmacy, Pharmacology, Chemistry, Physiology, Biochemistry and many of the fields allied with each. It is aided by subcommittees, special advisory boards and other groups of authorities on particular topics or in special fields such as the hormones, anti-anemia preparations, etc., even reaching so far as to include problems of packaging of drugs to prevent change or deterioration during storage. As an illustration, considerable research was required to determine the composition, color and thickness of glass to permit the establishment of proper specifications for bottles, ampoules and similar containers. Even the services of statisticians have been utilized in the further perfection of assay methods. In brief, there are few branches of modern scientific knowledge which have not been called upon to participate in the preparation of the forthcoming U.S.P. XII.

The selection of agents on the basis of therapeutic usefulness, or the rejection of others, is entrusted to a group of medical authorities and teachers who compose the Sub-committee on Scope. This committee is empowered to secure help and advice from any available source so that its final selections, while doubtless not perfect, are certainly representative of the best current scientific judgment. The Committee on Scope has tried to evaluate both the agents themselves and such preparations of them as are made available and has endeavored to restrict inclusion of preparations to those proved therapeutically most useful and satisfactory. In so doing the range of preparations or even of similar agents has been made wide enough to meet all medical needs. For example the group of hypnotics extends from those whose actions are rapid to those which act slowly; from those having relatively brief action to those which act for many hours; from those which may be administered by mouth to those which may be used parenterally, etc. The patient's requirements thus can be met if his physician knows both his therapeutics and his Pharmacopœia. The practitioner failing to find in the Pharmacopœia a drug which he has previously prescribed would do well to restrain any feelings of resentment until he has made certain that the official drugs will not serve him and his patient quite as well, or probably even better than his old favorite or one that is not official.

As a result of studied and scientific limitation both of drugs admitted and of the number of preparations of any single drug or therapeutic class of drugs the Pharmacopœia does much to simplify the physician's task of prescribing. Furthermore, complex mixtures are not included. Of course the prescriber is left entirely to his own medical judgment in his use of the drugs. He may prescribe them singly or in any combination which appears to him most suitable. In effecting combinations the physician has access in the text to information which will enable him to avoid incompatibilities of chemical and physical nature. The description of each drug states its important physical properties, its

chemical composition, solubility and any other characteristics which may influence its use in prescriptions.

Pleasant vehicles are described, along with their formulæ. With accurate knowledge of the drug thus at hand an appropriate vehicle may be chosen. But the U.S.P. XII goes even further and offers tablets, capsules and other dosage forms for many drugs. It even sets standards and specifies suitable menstrua for the solution or suspension of drugs which may be administered parenterally and recommends appropriate concentrations of the contained drug. It has been urged that the monographs which make up the major part of the volume, so far as it interests physicians, should include suggestions and recommendations regarding the therapeutic usefulness of each drug, or at least of those of recent introduction. This idea wisely has been rejected as outside the scope of a book of descriptions, standards and tests to insure constancy of therapeutic agents. Therapeutic usefulness of a drug is a matter of pharmacopœial concern only so far as it bears upon the problem of inclusion of a drug in the Pharmacopœia. Beyond that the therapeutic responsibility of the Revision Committee ends.

The Committee of Revision has established and stated average doses for substances intended for therapeutic purposes in conformity with a resolution of the Convention: "to state, where feasible, the average (neither minimum nor maximum) dose for adults, and, where deemed advisable, also for children. The term 'average dose' is to be interpreted as the dose which might reasonably be expected to produce the therapeutic effect for which the substance is most commonly employed." It is further stated expressly that these doses are not binding upon the physician who may exceed them whenever his judgment renders that advisable. Again the Convention has intentionally avoided an important therapeutic problem which is exclusively for the physician to solve for each individual patient. The statement of dose is made solely as a guide to the best accumulated experience and wholly without any implied recommendation. The doses were determined by vote of a large number of recognized authorities, and in some instances advice was obtained from the members of the special board concerned, such as the Anti-anemia Board, or the Hormone Board. The practitioner is thus guided authoritatively yet left free to use his own best judgment.

Potent remedies are made to conform, so far as is advisable, to international standards as established by the International Protocol of Pharmacopœial Experts. Wherever possible potency is based upon chemical methods of assay. There are many substances for which this is not yet possible and for these some biologic method is required. A vast amount of study has been given to the final selection of the particular method so that it shall be the best available at the time of publication. More will be said on this subject later, but the medical profession owes much to the labors of the Sub-committee on Bioassay which is responsible for choice of method, for its critical analysis and testing and for the detailed directions for its actual performance.

These represent only a few illustrations of what the Pharmacopœia means to the physician if he would but avail himself of its many services to his daily needs. The price of the new revision will presumably be higher than that charged for its predecessor, to which doubtless there will be some objections, however unjustified they may be. The

fact is that the revenue from sales covers only a small fraction of the total cost of revision. Several hundred thousands of dollars have been spent on research alone, most of which has been contributed by manufacturers, institutions of learning, government and other laboratories, etc., both in money and in the form of facilities and the skill and labors of those who have graciously and faithfully devoted themselves to the many and often complex tasks involved. A debt of profound gratitude is due to all who have so generously given of their funds and labors to make the volume as nearly perfect as possible. The price would be utterly prohibitive if it were based upon the actual costs of revision. Physicians can discharge this debt by making full use of the U.S.P. as a reference work of great value to them within daily practice.

We may now turn from the general to the specific and comment upon particular aspects of the Pharmacopœia.

Biologic Standardization. One of the most vital activities of pharmacopœial revision relates to the biologic standardization of drugs. Some of the most useful agents in the realm of therapeutics belong in this group. They are materials which vary in potency from batch to batch and for which there exist no chemical tests of potency. Without security that their strength is uniform, there is chaos in therapeutics.

The problem involves the testing of materials on animals and adjusting the finished product in such a manner that a given amount of different batches will produce the same effect. The group of therapeutic agents in daily use which requires biologic standardization includes the following: digitalis and preparations related to it, ergot, epinephrine, solution of posterior pituitary, parathyroid, insulin, estrogenic and pituitary materials, some of the vitamins, anti-anemia products (liver), serums and antitoxins.

The magnitude of the problem of establishing suitable methods of biologic standardization is not generally appreciated by the practising physician, although he may be fully aware of its importance. Animals that are used for standardization, like humans, vary in their sensitiveness to drugs. Even the average response for a group of animals may differ from the average response for another group tested under somewhat different conditions and by different bio-assayists. Furthermore, not all species of animals behave alike in response to certain drugs. For example, when preparations of digitalis are compared in the frog one often obtains results which are different from the results obtained in a similar comparison using cats. The selection of the most appropriate method is one of the major problems, since for most products numerous methods are described in the scientific literature. An endeavor is made, by comparisons in humans, to select that animal method which gives results most nearly applicable to humans. Sometimes slight variations in the details of the technique will yield different results. The method needs to be described in such detail as to insure similar results in the hands of bio-assayists in different parts of the country. The Pharmacopœia has the effect of law. The method must be so devised and described that different manufacturers of similar products may feel secure that they comply with the standard requirements of the Pharmacopœia since they are liable to prosecution if a product, labeled "U.S.P.," fails on reëxamination to comply strictly with its standard. The Pharmacopœia takes every measure available to insure uniformity of a product. Animal studies have shown that

the most uniform results are obtained if a product of commerce is compared with a standard material and the result expressed in terms of the standard. The Pharmacopœia supplies these standard materials to bio-assayists in the case of drugs for which standard materials exist. The Pharmacopœia has availed itself of the developments in statistical methods of the analysis of data in biologic standardization. Such analyses not only enable the bio-assayist to determine how potent a given material is in relation to the standard product, but to ascertain further the reliability of the standardization, the degree of likelihood that a given result is correct and not accidental. If, in a given case, the index of reliability as established by the statistical device is too low, the Pharmacopœia requires that the assay be repeated or improved. This technique has been applied to some of the biologic standardizations. The use of statistical methods marks a great advance in the safeguards for insuring uniformity in the strength of the medicinal agents of pharmacopœial status.

Insulin. The properties of insulin are such as to necessitate its most accurate and meticulous control. This has been exercised faithfully and efficiently by the Canadian owners of the patent. The recent expiration of the patent would have left the public unprotected against exploitation by careless or unscrupulous manufacturers and importers of the life-saving, yet potentially dangerous therapeutic agent, had this Revision Committee and the Board of Trustees of the U.S.P. not been alert to the situation. Insulin was made official in U.S.P. XI, the current Pharmacopœia, by the issuance of an Interim Supplement to cover the period between the expiration of the patent and the publication of the forthcoming twelfth revision, which will probably become official early in the autumn of 1942. By a special act of Congress the definition, description, strength, methods of assay, tests for purity, packaging and other details for control as given in the monograph contained in the supplement have become the law which will insure to physicians and the laity the future continued supply of a completely trustworthy insulin. Without such action the governmental authorities would have been without legal standards for the protection of the public against really great risks. An act of Congress now requires that each lot of insulin manufactured here or imported shall be checked by the Food and Drug Administration before it is released for distribution.

Digitalis. The twelfth revision of the Pharmacopœia has made extensive changes under the subject of the digitalis materials, in line with scientific developments of recent years. It has extended the scope to include not only basic preparations, but certain dosage forms. It now describes Powdered Digitalis, Tincture of Digitalis, Digitalis Capsules and Digitalis Tablets for oral administration. It also includes several preparations for intravenous and intramuscular administration, namely, the Digitalis Injection which describes in effect the ampoule of the purified mixture of digitalis glycosides. In addition, there is described the Ouabain Injection and Strophanthin Injection, as sterile solutions of these purified glycosides for parenteral use. The Pharmacopœia has therefore established standards for such a wide variety of preparations of digitalis materials as to meet every therapeutic need. The inclusion of capsules and tablets in the Pharmacopœia is a matter of considerable importance. It is one thing to establish a standard for the basic material and another to maintain that standard when the

material is put up into capsules or tablets, since in these inaccuracies may appear and the material may be altered by admixture with excipients and other cohesive materials. The Pharmacopœia describes the details of techniques by which the potent principles may be extracted from capsules and tablets for purposes of assay in order to insure that these dosage forms comply with the standard requirements.

One of the most serious problems in the use of digitalis preparations of commerce is the great multitude of products and the wide variety of potencies among them. The twelfth revision of the Pharmacopœia has established new safeguards to insure uniform potency among all the digitalis materials of Pharmacopœial status. The frog method has been replaced by the cat method as the official method of biologic assay. The two methods have been found to give different results regarding the relative potency of digitalis preparations. Extensive clinical experience and special experiments in humans designed to test which results are more applicable to man showed that the frog method is often misleading, and that the results by the cat method more nearly represent the relative potency of any two preparations in humans. This change was not made lightly. A special committee comprising cardiologists, bio-assayists and pharmacologists was established to study the problem. A detailed description of the new assay method was not only written but tested in a series of collaborative assays involving a large number of laboratories throughout the United States and Canada. After numerous corrections made as the result of these experiences with the method, it was found to give extraordinarily uniform results in the hands of different laboratories. In addition, a statistical device has been introduced by which the Pharmacopœia requires that the assayists not only secure an answer, but also an index of the likelihood that the answer is correct.

The greatest uniformity in the strength of digitalis preparations is assured by assaying these preparations against a standard material, the Digitalis Reference Standard of the Pharmacopœia, and 0.1 gm. ($1\frac{1}{2}$ gr.) of this digitalis power is defined by the Pharmacopœia as 1 U.S.P. Unit. The standard powder is supplied by the Pharmacopœia to those who standardize digitalis. The physician may then expect that if he administers 1 U.S.P. Unit of digitalis power, or of a tincture of digitalis, or of some water-soluble injectable solution, the effects of each in man will be identical, since each will represent the effect of one and the same thing, namely 0.1 gm. ($1\frac{1}{2}$ gr.) of the Digitalis Reference Standard. The amount by weight or measure matters little. In 1 case it might be 2 cc. of a solution, in another case 1 cc. What does matter is that the same amount of potent material is administered, and this can be secured by dosage in terms of U.S.P. Units. For those who have been thinking in terms of cat units, it might be stated that 0.1 gm. ($1\frac{1}{2}$ gr.) of the U.S.P. Digitalis Reference Standard or 1 U.S.P. Unit will represent approximately 1.3 cat units. In the case of the solutions of Ouabain and Strophanthin for parenteral administration, the dose of the drug is expressed in milligrams, without reference to any unit, and both are assayed against the Ouabain Reference Standard of the Pharmacopœia, a pure crystalline material.

There is little doubt that the changes which have been introduced into the forthcoming revision of the Pharmacopœia in relation to the

digitalis materials will greatly simplify their use and assure for their application in man a degree of uniform potency among market preparations such as has not been attained in the past.

Ether. The Pharmacopœia describes two qualities of ether. One is called "Ether," the other is called "Ethyl Oxide" or "Solvent Ether." More rigorous tests for purity are applied in the case of "Ether," since this is the only one to be used for the purpose of anesthesia. The article on anesthetic ether has in the past included a statement to the effect that ether to be used for anesthesia must be preserved only in small, well-closed containers, and is not to be used for this purpose if the original container has been opened longer than 24 hours. This caution was based on the belief that ether deteriorates very quickly when the container is opened, and under those conditions becomes unfit for anesthesia after 24 hours. The result of this requirement has been the purchase of ether by hospitals in very small containers of $\frac{1}{4}$ or $\frac{1}{2}$ pound. What remained unused for anesthesia was subsequently used for cleansing or solvent purposes. This was a very costly practice and one that resulted in great waste of highly purified anesthetic ether.

The forthcoming U.S.P. XII has revised this requirement. It allows ether to be used for anesthesia from containers with a capacity as large as 3 kg. Furthermore, it recognizes the fitness of the ether for anesthesia even after the container has been opened for an indefinite period. It is no longer therefore necessary to discard the costly anesthetic ether 24 hours after the container is opened. There is, however, the safeguard against deterioration in unsuitable containers in the requirement that ether is not to be used for anesthesia if it has been removed from the original container longer than 24 hours.

Scientific studies during the past several years have confirmed the fact that the metal containers in which anesthetic ether is supplied are of very high quality, that ether stored in them retains its purity indefinitely, and that in improperly prepared containers, deterioration is likely to take place fairly rapidly. The more recent studies have also shown that anesthetic ether in the metal containers in which it is supplied retains its purity for weeks and months even if the metal seal is removed and the container stoppered with cork. Experience involving thousands of surgical cases now exists in which it was found that bulk ether removed from cans which had been opened many times and stoppered with cork during a period of months produces a quality of anesthesia that is indistinguishable from that of the ether in a freshly opened can.

The Pharmacopœia has taken cognizance of these developments in its revised standards for anesthetic ether. Several large hospitals in various parts of the United States are now using bulk ether for surgical anesthesia in this way. Anesthetic ether in bulk costs only about one-fifth as much as the same ether in the $\frac{1}{4}$ pound containers, a very considerable saving, since the yearly consumption of anesthetic ether in the United States amounts to about $1,000,000. This saving is accomplished without the slightest compromise with the efficacy of the anesthesia or the safety of the patient.

(To be continued in the November issue.)

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THE RÔLE OF ROENTGENOLOGIC EXAMINATION IN DIAGNOSIS.

PERCY BROWN,[2] in a review article, emphasizes the importance of the discovery of the Roentgen ray for the medical world. The ardent minds that first perceived in this new gift of physical science a latent promise to medicine seized on it eagerly and forthwith to adapt it as far as possible to clinical needs.

Considering nasal sinusitis, Grier[6] has shown that an antrum filled with polypoid tissue might exhibit the same image on the roentgenogram as one filled with pus. The knowledge that polyps were present in the nose or that pus was draining from the antrum would enable the roentgenologist who interpreted the roentgenologic characters to make the diagnosis. He believes that the diagnosis can be accomplished best in routine practice by correlation of the data from the rhinologic and roentgenologic examinations with full understanding of the limitations of roentgenologic examination. In the field of diagnosis, what this author pointed out as a requisite in this particular field applies generally. Primary roentgenologic examination must always be regarded as part of a coöperative effort, with mutual appreciation of the advantages and disadvantages of each individual method. Wherever such an arrangement has prevailed, devoid of exploitation of the advantages of the individual method by individuals, the most satisfactory results from the standpoint of the patient have been attained.

The basic factor in the advantage of primary examination with the aid of the Roentgen rays is exemplified in a statement of Graham[5] made in the discussion of the criteria of malignancy. He stated that all organs and tissues have an architectural plan which is looked on as being normal. Any deviation from this plan immediately raises the question of either a benign or malignant neoplastic process. Growth of the epithelial cells of the skin outward to form villus-like processes usually indicates a benign neoplasm; growth into the dermis or subcutaneous fat usually indicates a malignant neoplasm. Similarly in the intestine growth into the lumen of pedunculated masses usually indicates a benign lesion; if into the submucous or muscular coats, usually a malignant. This architectural derangement can be depicted in the roentgenogram in many types of pathologic processes and nearly all the facts that Graham established as indicative of the nature of a lesion can be elicited in Roentgen examination. He recognized the necessity of correlation of the data of the physical and all other examinations with that of the pathologic study in the establishment of the ultimate diagnosis. The significant note of his presentation was that on the basis of accumulated experience certain conclusions were accepted generally.

Another advantage of roentgenologic examination as an aid in diagnosis was pointed out by Rigler[9] in the report of a roentgenologic sign of pneumoperitoneum, hitherto not reported or at least not clearly defined. A definite outlining of the outer and inner parts of the intestinal wall by the accumulation of gas between the loops of the bowel might depict the first evidence of the presence of pneumoperitoneum in some cases in which such a condition was entirely unsuspected.

In roentgenologic study of acute infections of the respiratory tract of children, Bouslog[1] divided the respiratory tract at the lower end of the pharynx into upper and lower portions that have anatomic and physiologic distinctions. While the mastoid processes do not aid in the preparation of the air for the lungs, they are directly connected with this upper part through the Eustachian tube; they were therefore included as a part of this tract. The pharynx, he believed, had a specialized and distinct function which was chiefly mechanical, involving the sphincter action of the glottis in governing the quantity and pressure of the intake of air. Physiologically, each division of the respiratory tract played a more or less independent rôle and had a somewhat dissimilar function to perform, but all functioned in harmony. Their chief use was to facilitate the passage of the air to the alveoli. The air was filtered and heated in the upper part of the respiratory tract to prepare it for oxygenation of the blood and distribution to the tissues concerned in this procedure. He pointed out that Mullin and Ryder had demonstrated the connection of the lymph drainage of the upper air passages and accessory sinuses with the lungs. He credited Pfahler with having demonstrated roentgenologically the lymph drainage from the maxillary sinuses to the thoracic duct by injection of lipiodol into the maxillary sinuses. Bouslog was of the opinion that a study of the mastoids, sinuses and thorax of all patients having acute infections of the respiratory tract would not only elicit a better understanding of the underlying pathologic processes, but also would give a better interpretation of the presenting signs and symptoms and thus permit intelligent treatment of such patients. With the belief that the mastoids and sinuses were involved more frequently than was generally realized, and the knowledge that a great majority of infants afflicted with severe gastro-intestinal disturbances as the outstanding symptom also have accompanying foci of infection in the mastoids, he studied a series of cases of acute infection of one of the divisions of the respiratory tract.

The conclusions from this study were that frequently acute infections in some division of the respiratory tract were more serious than the infection in another division which had been regarded as the factor producing the symptoms. Early, accurate diagnosis of such infections and adequate treatment, Bouslog thought, might prevent the occurrence of some of the chronic diseases of adult life.

In an article on intrathoracic neurogenic tumors, Kornblum and Bradshaw[7] brought out once more the value of Roentgen ray examination of the thorax, and that Roentgen examination afforded the best means of detecting intrathoracic neoplasms. They stated that the signs and symptoms of these lesions were often few and slight and frequently were lacking entirely. They remarked that it was astounding how large a tumor within the thorax might become before giving rise to

symptoms; such tumors have been accidentally discovered in routine examinations. They pointed out certain clinical and roentgenologic features which served to distinguish one tumor from another so that a critical correlation of roentgenograms with clinical signs often serve to establish a correct diagnosis.

Kornblum and Bradshaw asserted that neurogenic tumors of the thorax did not appear to have any predilection for sex or age. The clinical manifestations were not striking in most instances. The onset of symptoms was usually insidious. The rapidity of the course depended largely on whether the tumor was benign or malignant. The symptoms, largely those of pressure, were dependent on the structures on which pressure was exerted. The majority of neurogenic tumors occurred in the posterior part of the thorax, well away from any of the vital structures contained in the mediastinum. Here they might attain a considerable size before giving rise to manifestations of pressure.

Among the more constant and prominent symptoms were pain in the thorax and cough, either perhaps predominating. Because of their size, many of these tumors caused interference with normal pulmonary physiologic procedures by pressure. Interference with drainage of the lungs and the occurrence of atelectasis invited infection. Atelectasis was more prone to occur with tumors arising in the mediastinum which permitted the larger bronchi to be compressed. This was likewise true of pleural effusion, which was occasionally encountered. Paralysis of the phrenic nerve was also a manifestation of a mediastinal origin of the tumor. It was possible for a tumor to arise in the thorax and project into the vertebral canal.

These authors recommended that the routine Roentgen investigation for intrathoracic neoplasms should include a careful roentgenoscopic observation and an adequate roentgenographic study.

Considering the differential diagnosis, Kornblum and Bradshaw stated that lymphoblastoma, Hodgkin's disease and lymphosarcoma usually were confined to the mediastinum and produced in it a nodular enlargement. Lymphatic enlargements elsewhere in the body, from which specimens could be taken for biopsy, served as an aid in establishing the diagnosis. The rather prompt and striking response of lymphoblastoma to irradiation offered a valuable aid to diagnosis, in that the neurogenic tumors were highly radioresistant. Their experience had been that when lymphatic leukemia produced a pathologic change in the mediastinum, it was practically never an isolated process. A study of the morphology of the blood cells would reveal the true nature of the disease when lymphatic leukemia was present. Aneurysm of the thoracic aorta could be recognized most frequently by establishing its origin from the aorta in roentgenoscopic observation. Thymomas, in their experience, were confined to the mediastinum and their outlines in roentgenograms were usually irregular in contrast to the sharply demarcated shadow of the dermoid cyst. The thymoma, dermoid cyst and substernal or intrathoracic goiter occurred anteriorly in contradistinction to the posterior location of the neurogenic tumor. The goiter frequently compressed or caused deviation of the trachea and could be observed on roentgenoscopic study to alter its position with deglutition. Single, large, isolated malignant metastatic nodules, and intrathoracic fibromas or lipomas might be difficult to distinguish

from neurogenic tumors. The making of the differential diagnosis could be important, because the only treatment that was of any avail in neurogenic tumors was surgical removal.

The frequency with which the respiratory tract and such other sites as the gastro-intestinal tract, the skeletal system and the genito-urinary tract were affected by lymphoid diseases is not well recognized. This statement was made by Vieta and Craver[10] after a study of 1911 cases. Of this group of 1911 cases, they found that 794 were acceptable for roentgenographic study and 160 for an analysis of findings obtained at necropsy. Necropsy revealed that the incidence of intrathoracic lesions was much higher than was indicated by the roentgenographic studies that were made. These authors were of the opinion that more frequent Roentgen examination of the thorax was indicated by their study. The roentgenographic features lent themselves to analysis in subgroups as follows: 1, mediastinal tumor; 2, infiltration into the parenchyma of the lungs; 3, isolated nodules in the parenchyma; and 4, discrete nodules at the roots of the lungs. They also added two further subgroups, pleural thickening and pleural effusion. In their series they did not notice any particular frequency of enlargement of the right paratracheal nodes in Hodgkin's disease. Infiltrations into the parenchyma of the lungs, extending out from the hilus, considered diagnostic by some, occurred also in their experience in sarcoid of Boeck, tuberculosis of the tracheobronchial lymph nodes and metastatic carcinoma. They quoted Lenk as having observed that the clinical picture of tuberculosis in conjunction with the Roentgen characters of malignant tumor favored a diagnosis of Hodgkin's disease. Isolated nodules in the lung, almost invariably accompanied by one or more of the other types of intrathoracic manifestations of lymphoid disease, they considered as true metastasis after consideration of the fact that the Hodgkin's process must be disseminated through the body, either through the blood or lymph channels, to reach the bones and the structures of the nervous system, both of which are grossly devoid of lymphoid elements.

In a study of 335 cases, Vieta and Craver found mediastinal tumors in 47.4%, infiltration into the parenchyma of the lung in 38.5%, isolated nodules in 5.3%, discrete nodules at the roots of the lungs in 23.8%, pleural thickening in 7.4% and pleural effusion in 15.8%.

From the roentgenographic study these authors were impressed by the frequency with which intrathoracic structures were involved in Hodgkin's disease. The protean features of the lesions, however, led to the conclusion that there were no specific roentgenologic features that would allow the roentgenologist to make more than a presumptive diagnosis of lymphoid disease. In their experience, the lungs were probably more often invaded than any other structure with the exception of the lymph nodes. In 335 cases observed clinically and pathologically in their series, they did not find a single case in which they could state definitely that the parenchyma of the lungs was involved primarily and that the other manifestations were secondary. In about 7% of their cases the first Roentgen examination of the thorax revealed involvement of the mediastinum, hilus or parenchyma of the lungs. There were no cases of primary involvement of the pleura by Hodgkin's disease in their series. In 88% of the 51 cases in their series in which

necropsy was performed, they found some form of lesion within the thorax caused by Hodgkin's disease.

In malignant tumors of the lymphatic system (reticulum cell sarcoma, malignant lymphocytoma and giant follicular lymphadenopathy) the roentgenographic features were not unlike those of Hodgkin's disease. Displacement of intrathoracic structures, even when the mediastinal or hilar masses were of large size, was rarely noted in lymphosarcoma. Pleural effusion occurred in 16.6% of the cases observed; pleural thickening in 9.6%. Pulmonary involvement or pleural manifestations usually occurred rather late in the course of lymphosarcoma, but despite this, in many cases striking improvement in the patient's general condition followed irradiation of the affected regions. They were of the opinion that, when parenchymal involvement was noted, Roentgen therapy should be used to the full limit. When lymphosarcoma had invaded the intrathoracic structures, the involvement was widespread with the formation of large masses of neoplastic tissue. Their material obtained at necropsy indicated that in 30% of the cases infiltration of the parietal pleura was extensive.

In their roentgenographic study of lymphatic leukemia Vieta and Craver were impressed by the frequency of the parenchymal infiltrations in the lung. Involvement of the mediastinal and hilar nodes occurred most frequently, but at necropsy these nodes were of such dimensions that they would not have been demonstrable roentgenographically. Isolated nodules of leukemic tissue within the parenchyma in lymphatic leukemia were rare phenomena in their experience. In their roentgenographic studies, Vieta and Craver did not find an instance of a mediastinal tumor in a case of myelogenous leukemia.

Dusts as an industrial hazard have had much to do with the ever-widening interest of the directors of industrial corporations in routine Roentgen ray examination of the thorax as a requisite in preëmployment investigations and in connection with arrangements for the maintenance of the health and efficiency of employees. The commanding position of the roentgenogram in establishing a criterion for the awarding of compensation was exemplified by Clement[3] in a study of rock drillers in underground mines and of the conditions under which these miners worked. Follow-up investigations had included consultation with personal physicians of the miners and their families. Persons who had certain types of thoracic roentgenograms did not become disabled but were content in their employment and were able to do a full day's work. Thoracic shadows in such cases, the author pointed out, were not significant of damage that would entitle the person to compensation for disability. Because of the number of times that such illustrations had been used to support the idea of rock dust as an industrial hazard, he was of the opinion that insufficient correlation of data had resulted in false concepts of the significance of the roentgenographic shadows.

Doughty[4] stated that roentgenologic studies of the lungs afford the most accurate means of diagnosis of silicosis and that serial roentgenograms allow watching the changes as they occur. Although he acknowledged that physicians of large experience in all phases of silicosis, if given the number of years a worker has been employed, an accurate dust count of the air that the individual has breathed and the size of the particles of silicon dioxide in that dust, or if permitted to see a

group of employees walking up a moderate grade to work, could describe accurately the pathologic changes present in the thorax, he still maintained that most competent roentgenologists could achieve a much better average in the diagnosis of silicosis. Their success would necessitate adherence to the usual procedure recognized by the roentgenologist, namely 1, primary roentgenographic examination of the thorax and, 2, correlation of the roentgenologic data with that of, *a*, an accurate history of the subject's employment during his working life, *b*, an accurate dust count made at the breathing level of the patient, *c*, the percentage of silicon dioxide in the atmosphere breathed and the size of the particles present and, *d*, the findings in the taking of the medical history and the making of the physical examination. Although he acknowledged that a positive diagnosis of silicosis should not be made on the roentgenographic evidence alone, Doughty was of the opinion that an accurate diagnosis of silicosis was not possible without Roentgen examination of the thorax. This author quoted Burge, as follows: "Only the physician who has examined the subject, has obtained an occupational history of an adequate exposure to silica dust, and had before him a suitable roentgenogram of the chest, should make a diagnosis of silicosis. The roentgenologist not in possession of these facts can merely state whether the shadows which he sees in the roentgenogram are consistent with his diagnosis." He emphasized that demonstration of discrete nodules was the one essential in establishing the diagnosis of silicosis. Coalescent nodulation occurred when the nodules became numerous in a fairly small area and the fibrous tissue between them became more evident. He stated that coalescent areas were most commonly seen in the upper central portions of the pulmonary fields, and were almost always bilateral and symmetrically placed. Conglomerate masses usually were due to the merging of a number of these coalescent areas, with the addition of fibrous tissue, into a dense area of larger size. They, too, were usually in the central and upper portions of the pulmonary fields, although they sometimes occupied the greater part of the upper two-thirds of one or both sides. While these infiltrated areas were usually regular, his experience was that at times they might be irregular.

With this concise description of the pathognomonic roentgenographic features of silicosis, Doughty contended that in the follow-up work among employees of dusty industries, serial roentgenograms made every 6 months or every year were more valuable than the data of any other examination. They made an invaluable record for comparison. If in any later roentgenogram the number of silicotic nodules had lessened, then silicosis as a factor in the symptoms could be eliminated. Once established, these nodules never disappeared although they might be obscured as a result of active infection or massive formation of fibrotic tissue.

Complications might alter the roentgenographic image. Emphysema, seen commonly in the older and more advanced cases, began usually in the costophrenic angles and progressed along the diaphragm until it sometimes had occupied the lower fourth or third of the thoracic cage. It was almost always bilateral and symmetrical, in extreme cases with perhaps more lobules on one side than the other. Smaller amounts of emphysema were at times seen in the pulmonary fields surrounding

coalescent or conglomerate areas in the upper and middle sections. Fibrous bands were common in the advanced cases, extending from the dense masses in the upper portions of the lungs through the emphysematous region, causing tenting or peaking of the diaphragm where they were adherent. For some unexplained reason, Doughty found pulmonary tuberculosis to be more common and the mortality rate from it higher in the silicotic than it was in the general population. It was, in his experience, the most common cause of death among patients who had silicosis.

With the advent of industrial compensation in many states, a large number of the older employees in industries where they were exposed to certain forms of dust applied for compensation because of permanent total disability. This author, after a number of years spent in contact with these workers, in which his respect for their stamina and integrity was greatly increased, conceded the justice of their claims. Many of these older employees continued to work long past the time when they should have stopped. Many had advanced silicosis, usually complicated by pulmonary tuberculosis, either active or, more commonly, of the chronic fibroid type. Others showed evidences of the massive conglomerate type of silicosis with associated emphysema, at times complicated by cor pulmonale. Many, however, showed only evidences of simple, uncomplicated silicosis which in itself was not disabling. They were the victims of advancing age, and at the end of many years of hard physical labor they showed the effects of its toll on the human body. The problem of the physician was to determine whether or not silicosis played a part in their disability. The physician fortunate enough to have a series of roentgenograms of the individual concerned extending over a period of 8 or 10 years would find them of great value in the correct analysis of the individual case.

In differential diagnosis of early or moderately advanced cases, many conditions had to be considered such as anthracosis, siderosis, miliary tuberculosis, small metastatic, neoplasms especially of hypernephroma, many of the yeast fungi deposits, sarcoid of Boeck and sprue. In the more advanced cases, pulmonary tuberculosis, cancer, emphysema, bronchiectasis, atelectasis and the pulmonary changes of advancing age had to be considered. With advancing age there was more fibrous tissue in the lungs and the lymph vessels themselves were normally more evident. The roentgenographic image of chronic cardiac disease with the usual accompanying arteriosclerosis and pulmonary changes accompanying compensation might simulate that of silicosis.

Lemon[8] has stated that all particulate matter in the parenchyma of the lung is disposed of in essentially the same manner and that many particles, both organic and inorganic, were segregated into nodules. Of the inorganic substances, silica (SiO_2) was the most important because it constituted the greatest hazard in the dusty trades; of organic substances, the *Mycobacterium tuberculosis* was the most important because of the important disease it causes. Except for this organism, its reproductive powers, virulence and the allergic reactions it engenders, the response of the reticulo-endothelial system to its presence is substantially the same as the reaction to silicon dioxide. Experimental investigation had proved that silicon dioxide was the specific cause of the disease silicosis. He and his collaborators had found that graphite,

sericite, asbestos, granite and other substances containing silicon dioxide in small concentrations did not, under experimental conditions, produce specific nodular fibrosis, but rather a generalized fibrosis as seen in many conditions classified under the general term "pneumoconiosis." This author[8] stated that for many years observers had believed that diluents such as coal dust diminished the liability of exposed miners to clinically active tuberculosis. The same idea was applied to silicosis, and for years it was accepted as fact that coal dust acted as an inhibitor to the action of silica. He quoted clinical studies and experimental findings of many observers which seem to substantiate with some degree of certainty the concept that diluent dusts prevent, delay or modify the action of siliceous dust.

Investigation of the size of the particles showed that all observers were in agreement as to the size of the particles of silica that caused damage by becoming arrested within the lungs; these particles must not be too large for phagocytosis by the mononuclear phagocytic cells. The extreme limit in size proved to be 10 μ, and in well-ground quartz and in the dust of mines and dusty trades these large particles were relatively few. To be most effective and most dangerous, the particles measured from 1 to 3 μ. It was possible that these extremely small particles passed in and out of the lung with the air inspired or expired. Those that became arrested were probably very damaging because the degree of damage was, within certain limits, inversely proportional to the size of the particle.

In a study of the specific cell defending the lung against damage, it was determined that silicosis as a disease did not occur because silica was breathed into the lungs, but rather because sufficient dangerous particles were retained within the lung. The disease represented a defect of the defense mechanism resulting in the arrest of the phagocytes after phagocytosis had taken place, and formation of the specific fibrous nodule represented the effort of the organism to segregate, localize and encapsulate the noxious substance so that the least possible degree of harm might result to embarrass respiratory function. Phagocytosis took place largely in the alveoli, not in the larger air passages, and it was from the alveoli that the process of elimination began. The laden phagocytes floated in the serum that escaped from the capillaries, or they migrated along the walls of the alveoli by ameboid movement. In experimental investigation, within a few hours, they were seen to crowd about the terminus of the alveolar duct, which was their first intrapulmonary point of arrest.

Two paths of exit were available for these laden cells: First, they might enter the bronchiole lumen, where changes in pressure and size of the air ducts hurried them along toward the bronchi. Ciliary movements, entanglement in mucus, and muscular action formed the laden cells into a bolus which was readily expelled by coughing. The particles that found exit obviously did not become arrested and did not produce lesions. The second route of removal was by way of the lymph vessels. The lymphatic system is composed of two parts: one superficial and passing toward the pleura, and one deep, following the bronchi and blood-vessels toward the hilus. Lemon and his collaborators proved that arrest occurred and lesions always developed along these systems. They found that laden cells constantly arrived at the

terminus of the alveolar duct and that the stimulation of connective tissue elements constantly augmented their numbers. Cells containing mitotic figures gave evidence that silica promoted hyperplasia in the tissue cell system. Many of these cells became arrested and formed aggregations that created the first cellular lesions, which were ultimately transformed into fibrous pseudotubercles. Thus anywhere along the interlobar fissures, aggregations might be formed in the course of the pulmonary vein. The pleural lymph vessels carried ingested particles to the bronchopulmonary and tracheobronchial nodes at the hilus, where arrest and concentration of cells created cellular nodules. In experimental silicosis, the laden phagocytes were not readily destroyed; they ultimately became replaced by white fibers and so created in these several situations true silicotic pseudotubercles.

Through the elimination process, Lemon found that the stimulation of the tissue cells continued and early fibrosis occurred along the routes taken by the lymph vessels. Like the primary lesions of pulmonary tuberculosis, all silicotic lesions, regardless of their duration, were subject to changes that operated both within and from the outside of the nodule. When the first concentration of cells formed a microscopic nodule, pressure changes within the lung packed the cells so closely together that they assumed a spherical shape. The cells in the core of the nodule began to undergo degenerative changes. Accumulations of fat occurred in all stages and increased with the size of the nodule. The amount of degenerative change seemed to depend also on the number of particles that were ingested, just as the degree of degenerative changes in the tubercle depends on the number of virulent organisms of tuberculosis within the phagocytes. Both particles of silica and tubercle bacilli are protoplasmic poisons and under experimental conditions both caused fatty degeneration. Later, it was found, the core of the nodule became hyaline or, as in the tubercle, calcium settled there and calcifie lesions formed.

The polarizing microscope showed that the particles were most numerous in the core of the nodule and that they became progressively fewer toward the periphery. Nodules of different ages frequently were found in the same section and constituted evidence of the constant changes that tended to destroy them, whether they were of short duration and still cellular, or of long duration and seemingly obliterated by concentric fibrous envelopes or calcification of the core. Observations supported the belief that the action of silica was continuous and that there was no time limit to the duration of the disease, silicosis, in which silica was the specific etiologic agent.

Under prolonged and continuous stimulation, even in the absence of superimposed infection, fibrous changes proceeded. The silica stimulated production of macrophages and fibroblasts. Microscopically discrete pseudotubercles created large conglomerate nodules, and all the perinodular pulmonary tissues were involved in fibrotic changes; the alveolar walls were thickened, the alveoli were compressed, and the bronchioles were deformed into slitlike fissures which were recognizable only because their mucosa and muscular layers had been preserved. These structures were separated by heavy layers of dense fibrous tissue.

When infection supervened, the resultant changes were observed to be similar to those seen in tuberculosilicosis among human beings or

even in simple fibrocaseous tuberculosis. The pseudotubercles were no longer discrete but were surrounded by granulation tissue. The parenchymal structures were no longer affected by inflammatory changes, but the finer structures were thickened and deformed and evidence of bronchitis and pneumonia was encountered commonly. As in tuberculosis, ulceration and necrosis progressed and erosion of the vessels and bronchi occurred. There was also the same tendency toward the formation of thrombi in blood-vessels and lymphatic vessels that was characteristic of tuberculosis produced experimentally by a similar intratracheal technique.

Experimentally produced silicosis, therefore, like silicosis found among human beings, resulted from the interaction of particulate silica and the tissue cell system of the lungs. The nature and the degree of the defense reactions depended on the size, the number and the mass of the particles of silica. The exact cause of the reaction was unknown, but it probably was brought about by the electrochemical effects induced by contact of the particle and the cytoplasm of phagocytic cells. The reaction probably proceeded because the laden cells were not killed but were preserved, and might be concentrated into aggregations of cells situated along the course of the lymphatic system of the lungs. Arrest occurred as a result of phagocytosis and failure on the part of the eliminating mechanism of the lung.

The pathognomonic criterion of experimentally produced silicosis was the discrete pseudotubercle which was pearly-white in color, glandular, subpleural or perivascular and peribronchial in situation and visible and palpable on cut section.

The morbid changes in lungs of experimental animals were controlled by encapsulation, calcification and obliteration by collagenous and reticular fibers. Superimposed infection increased fibrosis in the perinodular parenchyma caused ulceration and necrosis of bronchi and blood-vessels, and brought about the death of the animal by bronchitis, bronchopneumonia and empyema. Simple, uninfected silicosis affected the function of the lungs in proportion to the amount of fibrous tissue that developed, the consequent reduction of vital capacity and the secondary loss of cardiac compensation.

The outstanding feature of this series of presentations is a demonstration of the fact that in roentgenologic investigation opinions are based on the study of graphic evidence. The most rapid and at the same time most accurate means of determining the diagnosis and establishing the prognosis is roentgenologic examination at the time of the primary examination in all types of cases in which this procedure can be made applicable. Correlation of the data on the roentgenologic examination with the results of both clinical and experimental investigations seems to indicate this.

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PHYSIOLOGY.

PROCEEDINGS OF

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SESSION OF FEBRUARY 17, 1942

A Technique for Demonstrating an Antidiuretic Action of Minute Amounts of Pitressin. WILLIAM A. JEFFERS and MARY M. LIVEZEY (Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania). Single rats rendered diuretic by water, and alcohol in sedative dosage, constitute a satisfactory biologic test for the antidiuretic action of pitressin. It is 10 times more sensitive than Walker's test (Walker, A. M.: Am. J. Physiol., **127**, 519, 1939), in which he used the diuretic rabbit; however, the required dose per kilogram of test animal is essentially the same. As an assay technique, using the same number of injections, ours is at least as reliable as the multiple rat test of Burn (Burn, J. H.: Quart. J. Pharm. and Pharmacol., **4**, 517, 1931) and as other available tests for antidiuretic substances.

The Activity of the Descending Duodenum in Man During Nausea Produced by Caloric Stimulation of the Semicircular Canals. FRANZ J. INGELFINGER and ROBERT E. MOSS (Evans Memorial, Massachusetts Memorial Hospital, and Department of Medicine, Boston University School of Medicine, Boston, Mass.). A tandem two-balloon system can be "anchored" in the descending duodenum if the balloons are inflated simultaneously when one balloon lies distal, the other proximal to the mid-point of the descending duodenum. A continuous record of duodenal activity can then be taken.

The duodenal activity was recorded in 20 human subjects before, during and after caloric stimulation of the semicircular canals. This procedure produced varying degrees of nausea 13 times in 11 subjects. With the onset of nausea, the descending duodenum underwent a generalized contraction in 8 instances, the degree of the contraction being roughly proportional to the intensity of the nausea produced. In 3 subjects, who experienced a mild "uneasiness," the duodenum appeared to relax. In 2 subjects, vomiting movements obscured the record of duodenal activity.

In 9 subjects who had no nausea after labyrinthine stimulation duodenal activity remained unchanged. When morphine sulfate was given subcutaneously to 5 of these subjects, nausea occurred in each instance and was accompanied by a generalized duodenal contraction. This contraction, and the similar one observed during the nausea which followed labyrinthine excitation, involved both parts of the descending duodenum simultaneously. No reverse peristalsis was noted. Nevertheless, the contracting duodenum expelled both balloons into the stomach 6 times after caloric stimulation and 3 times after morphine.

It appears that nausea, whether produced by labyrinthine stimulation or by the administration of morphine, frequently is accompanied by a generalized contraction of the descending duodenum which tends to expel the duodenal contents into the stomach.

The Mechanism of the Secretion of Sulfanilamide by the Gastric Mucosa. HORACE W. DAVENPORT (Department of Physiology, University of Pennsylvania). When sulfanilamide is present in the plasma it is secreted into the gastric juice. The concentration ratio which is the concentration in the gastric juice divided by the concentration in the plasma has an average value of 2.6, and it varies inversely with the rate of secretion and directly with the plasma concentration. The fact that the concentration in the gastric juice is higher than that in the plasma appears to indicate that thermodynamic work is done on the drug in effecting the secretion. However, a determination of the activity coefficients of the drug in plasma and in gastric juice shows that the ratio of the activity coefficients is 1 to 2.6. Therefore the different concentrations of the drug in the two solutions are actually at or approaching equilibrium. On the basis of the assumption that the drug diffuses through the mucosa at a rate proportional to the difference in activities an equation has been derived which completely explains the gastric secretion of sulfanilamide.

Influence of Anesthetics on the Balance Between Chemoreceptor and Central Control of Respiration. R. D. DRIPPS, JR., and P. R. DUMKE (Department of Pharmacology, University of Pennsylvania). In decerebrate dogs and cats data were obtained, first, on the response of the respiratory center to inhalation of CO_2, and, second, on the response of the carotid and aortic body chemoreceptors to threshold doses of cyanide injected intravascularly. Original purpose was to determine whether chemoreceptor reflexes are exaggerated in dogs by chloralose; this was found to be the case since the response of the center was regularly diminished and the response of the chemoreceptors regularly elicited by smaller doses after chloralose. Ether, barbital, nembutal, and morphine were also tested in dogs, all these and chloralose, pentothal, and cyclopropane in cats. All drugs depressed the response of the center to CO_2 in both species; this was the only result common to all drugs in both animals. Barbital, like chloralose, exaggerated chemoreceptor activity in dogs, and barbital, morphine, and nembutal did this in cats; morphine in dogs had no consistent effect; nembutal and ether in dogs, and pentothal, cyclopropane, chloralose and ether in cats, diminished chemoreceptor activity. The influence of the narcotic must therefore be considered in the interpretation of experimental results in this field. A partial explanation of the exaggeration of chemoreceptor reflexes mentioned above is the presence of anoxemia resulting from depression of respiration, which occurred with every drug except ether. High O_2 content in the inspired air was found to raise the chemoreceptor threshold to cyanide while low O_2 content had the opposite effect. Summation of anoxic and cyanide stimulation of the chemoreceptors may therefore explain some of these results but it cannot account for the variations among the different depressant agents. Ether, the only drug that did not depress respiratory minute volume, was also the only one that depressed both of the responses in both species; ether must therefore stimulate respiration by other mechanisms among which reflexes aroused by pulmonary irritation deserve prominent consideration.

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Studies With the Electron Microscope. THOMAS F. ANDERSON* (RCA Laboratories, Camden, N. J.) Some of the recent studies with the electron microscope include:

1. The Structure of Elementary Bodies of Vaccinia (with J. E. SMADEL and R. H. GREEN). Vaccinia elementary bodies are roughly rectangular in shape (0.2 by 0.3 μ) and contain an internal structure within some sort of a limiting membrane.

2. The Structure and Characterization of Bacteriophages (with S. E. LURIA). A number of strains of anticoli phage were studied and their reactions *with E. coli* followed. "Sperm-shaped" bodies were present in all preparations but the size and internal structure of the "head" as well as the length and thickness of the "tail" were found to be characteristic of the strain of phage. The sizes of these particles correspond roughly to sizes determined by indirect methods. The phage particles seemed capable of adhering to *E. coli* either at the head or with the tail and as lysis progressed the bacteria appeared to be damaged and eventually, of course, to disintegrate.

3. Tissue and Nerve Fibers of the Cat (with G. H. SCOTT). It was found that a cat's nerve, freeze-dried and fixed, could be easily teased apart and mounted for study with the electron microscope, revealing single nerve fibers and connective tissue fibers. Details of the work will be reported elsewhere.

The Bacterial Cell as Shown by the Electron Microscope.—STUART MUDD, T. F. ANDERSON, H. E. MORTON, and K. POLEVITZKY (Departments of Bacteriology, Schools of Medicine and Dentistry, University of Pennsylvania, and RCA Manufacturing Company). Electron microscopic study of a wide variety of bacteria has shown that the bacterium is a cell, with a cell wall distinctly differentiated from inner fluid or potentially fluid protoplasm. Within the inner protoplasm structural differentiation in the form of discrete spheroidal or discoidal granules, or of less definitely circumscribed areas of relatively high density, may often be seen in the electron micrographs. Spores and flagella when present are clearly seen.

The inner protoplasm may be darkened selectively and often shrunken away from the cell wall by exposing the bacterium to solutions of heavy metal salts [*e. g.*, $AgNO_3$, $Ni(NO_3)_2$]. Exposure to $Pb(Ac)_2$ has sometimes injured the cell with resultant swelling and escape of protoplasm. These observations point to a possible technology of differential "staining" for electron microscopy, as well as a technique for making visible the effects of germicidal agents on the individual cell.

The specific deposition of antibody on bacterial cells and flagella may be detected through an increase in darkness, thickness and "fuzzi-

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ness" of the cell wall or flagella, respectively. Deposition of antibody can be seen to be a function of antibody concentration and of time of contact of antigen and antibody.

The Study of Viruses and Proteins With the Electron Microscope. LESLIE A. CHAMBERS (Eldridge Reeves Johnson Foundation for Medical Physics and Department of Pediatrics, University of Pennsylvania). A series of pictures made with the electron microscope in the Johnson Foundation were used to illustrate the kinds of information relating to proteins and viruses which may be obtained through use of the instrument. Data on size, shape, and interaction of large molecules may be taken directly from the electronmicrographs, when the limitations of adequate contrast and resolution (30 AU) permit. Some difficulties in the interpretation of density differences in the electron-shadowgraphs were considered.

Exploratory examination of infected chick allantoic fluids indicates that viruses can be identified in such media exactly as bacteria can be identified in smears by ordinary microscopy. Electronmicrographs of the viruses of influenza, equine encephalomyelitis, and herpes simplex were shown, as well as virus-like bodies present in nasal secretions during severe colds.

Carotid and Aortic Body Reflexes in Unanesthetized Dogs. J. G. WATT, P. R. DUMKE, and J. H. COMROE, JR. (Laboratory of Pharmacology, University of Pennsylvania). Experiments were performed on 7 trained dogs to determine: (*a*) if the carotid and aortic chemoreceptors are tonically active in the unanesthetized dog breathing room air; (*b*) if the respiratory center of the unanesthetized dog, deprived of carotid and aortic body reflexes, is stimulated by oxygen-lack. Unanesthetized dogs were used since the recent work of Dumke and Dripps (see p. 777 above) indicates that the results of experiments in this field may be dominated by the anesthetic.

Results. (*a*) Some chemoreceptors are continuously activated by the degree of oxygen unsaturation normally present in the arterial blood of the unanesthetized dog breathing room air, because inhalation of 100% oxygen regularly led to an immediate decrease in pulmonary ventilation. Respiration returned to normal in 1 to 6 minutes despite continued inhalation of 100% O_2, but during the sixth minute the arterial pCO_2 remained elevated (average increase 3.8 mm. Hg) in 5 out of 6 dogs. After chemoreceptor denervation inhalation of oxygen no longer decreased respiration, but either increased it or had no effect.

(*b*) Low oxygen mixtures which regularly increased breathing in the normal dog failed to do so after chemoreceptor denervation. A progressive depression of respiration on low O_2, followed by hyperpnea on changing back to room air was seen in most cases. The absence of stimulation in these unanesthetized denervated animals cannot be attributed to a failure of arterial pO_2 to fall, for with the same 14% O_2 mixture the average pO_2 in the denervated dog was 33 mm. Hg compared to 48 mm. in the intact animal. The primary effect of anoxemia upon the respiratory center of the dog is therefore depression.

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